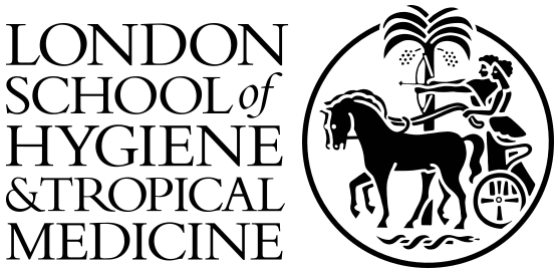

The epidemiology of infertility: measurement, prevalence and an investigation of early life and reproductive risk factors

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Declaration of own work

I, Laura Louise Oakley, confirm that the work presented in this thesis is my own.

Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signed:... [redacted] .....Date:.....10/03/11.....

Abstract

Estimated to affect one in six couples in the UK, infertility is an issue of great public health importance. This thesis provides a critical overview of the methodological issues in defining and studying infertility, and investigates the epidemiology of infertility, particularly prevalence and early life and reproductive risk factors. An initial literature review critically evaluated different approaches to defining and measuring infertility, and provided an overview of current prevalence, trends, and existing literature on the determinants of infertility.

Two datasets were analysed for the investigation of the epidemiology of infertility. The first was the Uppsala Birth Cohort Study Multigen, which describes the experiences of over 6000 Swedish women born between 1915 and 1929. Two indicators of fertility were used: general and age-specific fertility rates, and time to first live birth. These were analysed with respect to specific early life factors: gestation, birthweight, birthweight for gestational age, and ponderal index. The results provide no evidence to support the hypothesis that these markers of *in utero* growth are associated with fertility in adult women.

The second dataset was the National Women's Health Study, a population-based survey conducted in 2001 which collected information on the reproductive histories of over 7000 UK women. These data were used to describe the epidemiology of infertility in the UK, providing rarely reported data on the prevalence of infertility, help-seeking for fertility problems, and the use of treatment for fertility problems. The second stage of this work investigated the relationship between prior adverse reproductive outcomes and secondary infertility. The results suggest that secondary infertility is associated with prior adverse pregnancy outcome including termination, miscarriage and ectopic pregnancy, although with the exception of prior ectopic pregnancy, associations were weak and often inconsistent.

The implications of these findings, and recommendations for future studies on infertility, are discussed.

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Glossary

Term/acronym	Definition
Age-specific fertility rate (ASFR)	The number of live births per 1,000 women to a population of women within specific age bands in a given age range (often 15-45) in one year.
Assisted reproductive technology (ART)	The use of specific techniques to achieve conception by methods other than sexual intercourse. Includes intrauterine insemination (IUI), *in vitro* fertilisation (IVF), intracytoplasmic sperm injection (ICSI), artificial insemination (AI), frozen embryo replacement (FER) and gamete intrafallopian transfer (GIFT).
Birthweight by gestational age	Birthweight adjusted for gestational age.
Completed fertility rate	The number of children born per woman to a cohort of women by the end of their childbearing years.
Crude birth rate	The annual number of live births per 1000 population.
Fecundability	Probability of becoming pregnant in a given period.
Fecundity	Ability to achieve a live birth.
Fertility	Product of reproduction (demography). Capacity to conceive a pregnancy (also used more generally to indicate ability to achieve a live birth).
Fertility treatment	Any treatment designed to aid fertility, including donor-assisted conception, pharmacological treatment (for example, to induce or regulate ovulation), and more invasive techniques (e.g. ART). Also defined as treatment for any conditions known or thought to have an adverse affect on fertility.
General fertility rate (GFR)	The number of live births per 1,000 women in a given age range (often 15-45) in a given year.
Infecundity	Inability to achieve a live birth.
Infertility	Inability to conceive (also used more generally to indicate inability to achieve a live birth).

Term/acronym	Definition
Infertility treatment	[see 'fertility treatment']
Intrauterine device (IUD)	Contraceptive device that is fitted inside the uterus.
Involuntary childlessness	Inability to deliver a (wanted) child.
Lifetime prevalence	Ever experienced infertility/infecundity etc.
Pelvic inflammatory disease (PID)	Infection of the female reproductive organs. PID is caused by bacteria which passes up from the vagina to the cervix and uterus and can travel as far as the fallopian tubes and ovaries.
Polycystic ovary syndrome (PCOS)	Endocrine disorder characterised by multiple small cysts on the ovaries, excessive production and/or secretion of male hormones (hyperandrogenism), and absence of, or irregular, ovulation (oligo- or anovulation).
Ponderal index (PI)	A measure of weight relative to length (kg/m3), calculated using measurements taken at birth.
Primary infertility	Infertility in a woman/couple with no previous conceptions/live births.
Resolved infertility/infecundity	Infertility that did eventually result in conception/live birth.
Secondary infertility	Infertility in a woman/couple with previous conceptions/live births.
Small for gestational age (SGA)	Infants whose birthweight falls below an accepted threshold for their gestational age (most commonly defined as $<10^{th}$ percentile).
Sterility	Physiological state of complete inability to conceive.
Subfecundity	Reduced ability to achieve a live birth.
Subfertility	Reduced ability to get pregnant (also used more generally to indicate reduced ability to achieve a live birth).

Term/acronym	Definition
Time to first live birth (TTFLB)	Interval between first exposure to pregnancy (defined as beginning at marriage in the analyses reported in this thesis) and the birth of the first liveborn infant.
Time to pregnancy (TTP)	Interval between first exposure to pregnancy (usually defined by the start of unprotected sexual intercourse) and actual conception.
Total fertility rate (TFR)	Average number of children that would be born alive to a woman (or a group of women) during her lifetime if she were to pass through her childbearing years conforming to the age-specific fertility rates of a given year.
Unresolved infertility/infecundity	Infertility that has not (yet) resulted in conception/live birth.
Voluntary childlessness	State of being childless due to choice.

Chapter 1: Introduction and rationale

Infertility is associated with significant medical, social, economic and demographic consequences and as such is considered a major public health problem. The economic costs of infertility are characterised by the financial costs to individuals and the health services in terms of medical investigations and treatment, and also the costs of complications resulting from such treatment and the resulting births. There are also considerable psychological and social implications of both infertility and infertility-related services and treatment.

Not only do fertility problems affect a significant proportion of the population at some point in their lives, infertility remains an issue of great topical interest, with constant media reports 'alerting' the public about rising infertility. In particular, equitable access to help via the National Health Service (NHS) is a matter of constant debate. There is evidence that NICE guidance regarding entitlement to IVF is implemented inconsistently,[1] and given the scale of likely proposed cuts to the NHS, infertility services and treatment are likely to be significantly scaled back in the future.[2]

Estimates of infertility prevalence in the UK vary, but most figures suggest that between one in five and one in six of couples will experience difficulties conceiving.[3-8] Multiple factors affect estimates of prevalence, including methodological issues such as definitions used, trends towards delayed childbearing, differing patterns of help-seeking behaviour, and the increased use of medical treatment to aid fertility. Despite the relatively high proportion of couples who experience fertility problems, estimates suggest that true unresolved infertility (sterility) is a rare outcome.

The majority of infertility-related research has focused on treating the consequences of infertility rather than investigating the determinants themselves.[9] Infertility can be considered a characteristic of a couple, with female or male factors implicated, or in some cases, both. Some risk factors for infertility such as age and lifestyle factors have been the topic of considerable epidemiological research. However, other risk factors

have received little investigation. For example, little is known about the role of early life factors, an association which deserves more research given the epidemiological popularity of the 'fetal origins hypothesis' linking early life factors, particularly markers of *in utero* growth, to various health outcomes in adulthood. In addition, there is growing interest in the clustering of adverse reproductive outcomes across a woman's lifetime, but again little research has been conducted and there is a paucity of appropriate data with which to investigate hypothesised associations. The lack of knowledge with regard to determinants is compounded by inconsistent approaches to defining infertility and the variety of methodological approaches to studying infertility.

This thesis describes an epidemiological investigation of infertility, including both a critical overview of the methodological issues in defining and studying infertility, and an analytical investigation of the prevalence and determinants of infertility.

Chapter 2: Aims and objectives

The overarching aim of this thesis is to provide a critical overview of the epidemiology of, and methodological issues in defining and studying, infertility and to conduct an epidemiological investigation of infertility, concentrating on prevalence and early life and reproductive risk factors. The work will concentrate on female infertility but will include information on male infertility where relevant and appropriate.

2.1 AIMS

The four aims of this thesis are as follows:

1. To review the literature surrounding the definition and determinants of infertility.
2. To explore the hypothesis that *in utero* growth impacts on later fertility of women.
3. To measure the prevalence of infertility and use of infertility treatment in the UK.
4. To explore the hypothesis that one or more prior adverse reproductive events has an impact on secondary infertility in women.

Aim 1: specific objectives

To review the literature surrounding the definition and determinants of infertility. Specific objectives of this analysis will be:

- To critically evaluate current definitions of infertility.
- To provide an overview of current prevalence and trends in infertility.
- To review the literature regarding the determinants of infertility, with particular focus on early life and reproductive risk factors.

Aim 2: specific objectives

To explore the hypothesis that *in utero* growth impacts on later fertility of women. This will be tested using a cohort of women born 1915-1929 in Uppsala, Sweden (UBCoS – the Uppsala Birth Cohort Study). Specific objectives of this analysis will be:

- To describe the characteristics of this sample of women.
- To present and interpret general and age-specific fertility rates according to specific early life factors relating to *in utero* growth (preterm birth, low birthweight, small for gestational age status, and low ponderal index).
- To determine the effect of the above mentioned early life factors on estimated time to first birth among a sample of married women in the UBCoS cohort.

Aim 3: specific objectives

To measure the prevalence of infertility and use of infertility treatment in the UK. This will be investigated using National Women's Health Study (NWHS) data. Specific objectives of this analysis will be:

- To describe the characteristics of women in the NWHS cohort.
- To report prevalence estimates of infertility.
- To examine the similarities and differences in prevalence when using different measures of infertility.
- To describe trends in infertility by age.
- To describe the clinical diagnoses associated with infertility.
- To investigate the characteristics of women who seek and receive medical help for infertility.
- To measure the proportion of women who have treatment for infertility and who subsequently have a birth.
- To compare the observed and expected number of reproductive events ever experienced according to infertility status.

Aim 4: specific objectives

To explore the hypothesis that one or more prior adverse reproductive events has an impact on secondary infertility in women. This will be investigated using NWHS data. Specific objectives of this analysis will be:

- To explore the timing of secondary infertility in terms of ever and prior reproductive events.
- To determine whether prior adverse reproductive events are associated with the risk of secondary infertility.

Chapter 3: Overview of the epidemiology of infertility

This chapter contains a review of the literature surrounding the definition and determinants of infertility. In particular, the following objectives are addressed:

- To critically evaluate current definitions of infertility
- To provide an overview of current prevalence and trends in infertility
- To review the literature regarding the determinants of infertility, with particular focus on early life reproductive and risk factors

3.1 DEFINING INFERTILITY

Evidence suggests that on average, 84% of women exposed to regular unprotected sexual intercourse conceive within one year, rising to 92% and 93% respectively after two and three years.[10] This is what defines so-called 'natural' fertility in humans, and diversion from this natural, biological, expectation falls into the territory of infertility. However definitions of infertility are many and varied and research in this area has been hampered by a lack of a universally accepted definition of infertility, with 'infertility' being used interchangeably with terms such as 'sterility', 'subfertility' and 'subfecundity'.

"Current terminology is...ambiguous, confusing, and misleading" [11]

Terminology is at the heart of epidemiological investigations of infertility and a thorough discussion of the approaches to defining and measuring infertility is necessary before a consideration of trends and determinants of infertility can be offered.

3.1.1 Definitions: an introduction

The different terms used to conceptualise fertility have their origin in a diverse range of traditions. Demography, often described as the study of the characteristics of human populations, has a long history of describing fertility patterns. Demographers are primarily interested in population-based measures of fertility, usually the level and distribution of births in a population,[12] and often use the term 'sterility' for the proportion of the population that has not achieved a pregnancy after marriage. Common

demographic indicators include the number of births observed in a population (the crude birth rate or general fertility rate), the probability of conception among groups, and patterns of contraceptive use. The total fertility rate is another demographic measure of fertility 'performance', referring to the mean number of livebirths experienced by women during their lifetime or some other time period, sometimes presented by year of age. Demography has traditionally made use of routine data or other data based on the registration of births and deaths. The potentially voluntary nature of conception is usually not taken into account, nor are other factors that may affect fertility. As data on conceptions is rarely available, the focus is on births.

Over time, demographers have developed specialist terms used to describe fertility patterns. In the strictest sense, the term 'fecundity' is used to describe the reproductive capacity or potential of individuals (or, strictly speaking, couples) to achieve a live birth. The term 'fecundability' is used to denote the probability of a couple conceiving during a normal unprotected (no contraception used) menstrual cycle. Some of these terms are rarely used outside demography (such as 'fecundity' and 'fecundability'), but terms such as 'infertility' and 'sterility' which have their roots in demography have become part of mainstream terminology, though without the precise definitions acquired in demography. Central to the discussion of infertility is the concept of *voluntary* and *involuntary* infertility. The inability to conceive or deliver a liveborn child only becomes a problem when this outcome is desired. Differentiating between these two situations is difficult: a woman can experience both voluntary infertility and involuntary infertility over her lifetime.

Clinical definitions of infertility tend to be individual-based and are typically concerned with classifying an individual or couple as having a problem conceiving. From a clinical perspective, the need to predict the number of individuals or couples who will seek help because of problems conceiving has guided the measurement of infertility. Clinical definitions of infertility are usually characterised by a focus on the length of time a couple have unsuccessfully attempted to conceive, and setting a threshold above which failure to conceive is considered to be pathological, defined as a medical problem, and in need of investigation and/or treatment. The outcome of interest is invariably conception rather than birth. There is no definite agreement on how long such non-

conception should continue before being labelled as infertility. The classic clinical definition of infertility is based on the inability to conceive after a period of 12 months,[13-14] though the World Health Organisation (WHO) advocate using a minimum period of 24 months.[15] It is a prerequisite of most (but not all) definitions that during the period of non-conception, regular sexual intercourse should be taking place with no use of contraception. Subfertility is another term frequently used within clinical medicine, used to describe those who have a reduced capacity to conceive.

Some definitions of infertility have used as a starting point the number of individuals or couples who seek help because of problems conceiving. This measure of infertility is particularly useful from a clinical perspective, as it can be used to design and deliver appropriate services. This measure can further be broken down into the proportion of individuals or couples who seek help, and those who progress to receiving fertility treatment. Data on help-seeking and treatment can often be collected via clinical databases.

Epidemiologists have drawn on both demographic and clinical definitions. In general, epidemiologists are concerned with measures of prevalence and the investigation of risk factors and determinants. As such, a rigorous definition of infertility is needed, one that ideally reduces the number of false positives. One definition that meets this criterion is that of 'unresolved' infertility, potentially a good proxy of 'true' infertility. Unresolved infertility (also termed 'involuntary childlessness') can be defined as either failing to conceive a pregnancy or deliver a live birth (depending on the outcome). This is measured at the end of a woman's reproductive 'career', i.e. at or beyond her menopausal years.

Another measure of infertility commonly used in epidemiology is 'time to pregnancy' (TTP), defined as "the number of months that a couple takes to conceive, given unprotected intercourse".[16] This is considered to be equivalent to the number of menstrual cycles that a couple takes to conceive, with recognition that calendar months are more easily recalled by most women. This measure was first described by a demographer as far back as the 1920s.[12] The use of this measure increased during the late 1980s when it gained popularity as a functional measure of fertility, commonly

used in evaluating the effects of demographic, lifestyle, environmental and occupational exposures on, or 'hazards' to, fertility.[17] TTP is ideally measured prospectively, though it is often costly and impractical to conduct studies of this kind. Therefore, it has also commonly been investigated through retrospective self-report. The validity of retrospective recall of TTP has been confirmed, even when the duration of recall is ten years or more.[18-20] Questionnaires collecting data on retrospective TTP have been used in many different types of studies, and found to be acceptable across a wide range of cultures.[21] TTP has also been used as an indicator of infertility in historical populations, estimated as the interval between marriage and first birth, or the interval between subsequent births.[22-24] Although TTP can be used as a continuous measure (with mean TTP compared between groups), a common approach is to use a cut-off in order to derive a binary outcome. Twelve months is the most commonly used cut-off, although 24 months is also sometimes used. In this way, couples who take more than 12 or 24 months are considered to have impaired fertility, and those that conceive in less than this time are considered to have 'normal' fertility.

3.1.2 Strengths and limitations of different approaches to defining infertility

Each approach to defining and measuring infertility has strengths and limitations, and these need to be considered carefully. The choice of which measure to use will depend not just on methodological issues, but also on practical concerns, for example the availability of information and the suitability for the research question under study.

Conceptions verses births

The terminology relating to infertility is confusing to the extent that even the outcome of interest in infertility is not universally agreed – is it the failure to conceive a pregnancy, or the failure to deliver a livebirth which characterises infertility? The demographic tradition has focussed on birth as outcome; such studies often make use of routinely collected datasets in which births are accurately reported – there is no equivalent register of conceptions. This highlights the problematic nature of collecting information on conception. It is important to distinguish between the failure to conceive and the failure to deliver a liveborn child; the etiologies may vary and the implications differ. The two measures are not interchangeable. For example, a woman may have no problems conceiving but recurrent miscarriages may prevent her delivering a liveborn

child. Clinical medicine has traditionally been concerned with both outcomes (conception and live birth), but it has been argued that for individuals the most relevant outcome is birth.[25] After all, it is a child that potential parents desire, not a pregnancy that has a risk of ending in adverse outcome.

Primary verses secondary

Another key factor in evaluating the use of different definitions of infertility is the issue of whether the infertility is primary or secondary. 'Primary infertility' refers to infertility without previous pregnancy. Women or couples who have previously had a successful outcome (conception or livebirth) and then suffer difficulty in repeating the success are defined as experiencing 'secondary infertility'. The situation is complicated when a change in partner is present – it may be primary infertility for the couple but secondary infertility for the woman.

Voluntary versus involuntary childlessness

Although demography has a long history of describing fertility patterns, much of these data are of limited use in moving beyond descriptive analysis. There is a heavy reliance on population data, which limits the outcome to births. Such data are not able to account for the voluntary nature of childbearing: some of those who are childless are so by choice. This increases the difficulties associated with making cross-cultural and cross-cohort comparisons as factors influencing voluntary infertility are likely to differ. With only routine data it is also impossible to account for the influence of contraception and fertility treatment on population-wide prevalence of infertility. However, population fertility rates can be a useful way of assessing the effect of different exposures on fertility[26-27]; this approach is often used in the presentation of national routinely collected data and can be usefully compared across populations where most women desire children.

Length of time trying to conceive

As discussed previously, clinical definitions of infertility tend to rest on the number of months that a couple have been trying unsuccessfully to conceive. The thresholds used tend to be arbitrary – twelve months is often used, but it has been suggested that the threshold applied should be vary according to other characteristics. For example,

according to guidelines produced by the UK National Institute for Clinical Excellence (NICE) and the American Society for Reproductive Medicine, in women over the age of 35 failure to conceive within six months should be a criterion for further investigation.[14, 28] This perhaps reflects that clinical definitions of infertility are used for making decisions about service provision and treatment. There is strong evidence that subfertility increases with female age, so it would be expected that women over the age of 35 may take longer to conceive than their younger counterparts. However, the guidelines recommend that earlier investigations and treatments are warranted in the older age groups – it is imperative to intervene sooner in these cases as there is less time to provide assistance.

One particular problem with clinical definitions of infertility is that they overlook the fact that many couples who fail to conceive within 12 months go on to spontaneously conceive at some point in the future. One prospective study carried out in the Netherlands and based in primary care found 52.5% of couples with a history of >12 months non-conception had achieved a livebirth by 36 months.[29] One US prospective study reported that 23% of couples registered at an infertility centre (who had failed to conceive after a minimum of 12 months) had an apparently treatment-independent pregnancy.[30] In summary, clinical definitions represent another indicator of subfertility rather than infertility *per se*.

Seeking medical help for problems conceiving

The proportion of women or couples who seek medical help for fertility problems is sometimes taken as a proxy for the number who experience fertility problems. This is justified by the fact that there is in general good public awareness of infertility, and in the UK and many other developed countries, a health service free at the point of access means that the financial barriers to help-seeking are minimised. However, the reliability of this measure is questionable. The evidence suggests that on average, only half of those who experience problems conceiving seek help.[31] Those that seek help are likely to be a highly self-selected sample. The results of several small studies suggest that those that seek help are likely to more highly educated and from higher socioeconomic groups.[6, 32-33] However, this finding was not replicated in a recent analysis of NWHS (the National Women's Health Study) data carried out by myself and colleagues, which

suggested that there was little evidence of social inequalities in access to and receipt of fertility care and treatment.[34] There may also be a small proportion of women or couples who seek help before a problem is encountered, perhaps because of gynaecological conditions, or where there is a need to seek genetic counselling before attempting to conceive.

Unresolved infertility

Although 'unresolved infertility' has been described as a useful epidemiological indicator,[35] it is rarely used because of the difficulty in collecting data that can only be ascertained at the end of a woman's reproductive career. In addition, although national data registers can collect data on childlessness, they rarely contain the information necessary to distinguish voluntary childlessness from involuntary childlessness.

TTP

As mentioned previously, TTP is probably the most commonly used epidemiological indicator of infertility. Retrospective recall of TTP is the most frequently used approach for estimating the effect of specific exposures on fertility.[36] However, there are a number of specific limitations and biases associated with using TTP as a measure of infertility.

Crucially, TTP studies only look at those with resolved infertility. A conception has to take place in order for TTP to be measured or estimated: this immediately excludes women or couples who experience fertility problems which are not resolved. Therefore, in the strictest sense, studies which use TTP as the outcome estimate subfertility (problems trying to conceive) rather than infertility (inability to conceive).

It is theoretically possible for prospective TTP studies to follow couples 'at risk' of conception rather than those actively planning to conceive, but the vast majority of TTP studies only consider intended (or 'planned') pregnancies. This results in a number of methodological complications in addition to giving rise to possible bias – couples who plan pregnancies are likely to differ from those who do not.[37]

The classification of pregnancies as 'intended' is particularly problematic in studies that rely on retrospective recall. A range of terms have been used to capture this concept, including 'unwanted' vs. 'wanted', 'intended' vs. 'unintended', 'mistimed',[38] and there is little consensus in existing literature as to how any of these concepts should be defined.[39] As one author has stated:

> *"The definition of "trying to conceive" is subjective in that it implies a conscious desire to become pregnant that may not correspond well with behavior"* [40]

Recall bias may lead women to report that unintended pregnancies were indeed intended,[41] described by one author as "wantedness bias".[42] As a consequence, these unintended pregnancies would contribute to a disproportionate number of pregnancies with a very short TTP.[43]

Couples who experience unintended pregnancies tend to have higher than average fertility.[9] As one researcher suggests, where fertility is 'imperfectly controlled', couples who try to conceive tend to be less fertile, as more fertile couples conceive unintentionally.[38] This would lead to an under-representation of highly fertile couples in TTP studies. However, it has also been suggested that subfertile couples who are aware of problems may be inconsistent users of contraception and less likely to define themselves as actively trying to conceive.[9]

Ideally, well designed studies should collect information on a wide range of factors that may affect TTP. Timing and frequency of intercourse are some of the most obvious potential confounders.[9, 44] Prospective studies tend to offer better potential for collecting relevant data. One review suggests a list of data that would ideally be collected in prospective studies, including couple-level factors (e.g. age, medical history, semen analysis, occupational exposure), cycle-level factors (e.g. estimated day of ovulation), and day-level factors (e.g. sexual intercourse, markers of ovulation etc.).[41] Precise science with various statistical models to take into account of how these factors may vary is required. Reproductive history is another important potential confounder,[9] particularly given the tendency for women to include miscarriages in reports of long TTP.

It has been argued that censoring and truncation are a particular problem with TTP. One author comments that TTP data is not a representative sample of the distribution of TTP in a population, but only captures those TTPs which are not censored prior to being observed.[45] The TTP period is required to be short enough for conception to occur before the end of the study, but long enough for the time of conception to occur after study initiation.[45] For this reason, retrospective TTP studies may under-represent subfecund women with long times to pregnancy.[37] One proposed solution is to only study women/couples who have finished their reproductive careers. Alternatively, some authors suggest the use of statistical modelling approaches to deal with right truncation.[46] In a context where couples who experience problems conceiving seek medical advice, long TTPs may be unreliable.[19] Some studies choose to right censor after a TTP of 12 months to reflect that many couples begin to seek/receive treatment at this point.[42, 47-48]

TTP studies have occasionally observed spurious effects, most notably the tendency to find shorter TTPs associated with increasing maternal age.[9, 43, 49] Some authors have suggested that differential persistence may explain such results: older women may give up trying to conceive more readily than younger women and be lost from the denominator.[9, 46, 49] The authors of one study which reported such a trend suggest that the findings may be attributable to either bias resulting from the exclusion of sterile couples (perhaps sterility increases with age without an accompanying increase in TTP) or the exclusion of unplanned pregnancies (younger women may take more risks or use less effective contraceptive methods, and therefore be over-represented in unplanned pregnancies).[43]

Other issues that have been raised in relation to TTP studies include the lack of clear sampling frames for prospective studies.[46] Also, the tendency for retrospective studies to select participants via antenatal care settings has been criticised as introducing inherent selection bias.[41] It has been suggested that in order to minimise bias, retrospective TTP studies should be based on population-based surveys rather than volunteer studies.[46]

The usefulness of TTP in investigating time trends in infertility prevalence has also been challenged. One author has suggested that as contraception becomes even more effective and widely used, highly fertile couples may be less likely to conceive unintentionally. This would result in the proportion of highly fertile couples who are included in TTP studies decreasing over time.[17] The phrase 'protection bias' has been coined to describe the phenomenon whereby differential access to methods of preventing unintended pregnancies can affect estimates of the TTP distribution.[50]

Despite the limitations of using TTP as an indicator of infertility, studies that make use of such measures offer unparalleled opportunities for epidemiological investigations of infertility. They are straightforward to conduct, and particularly the retrospective designs, tend to be cheap and efficient. They are particularly useful as hypothesis-generating and exploratory studies, and for comparative studies investigating hazards to fertility. It has been argued that TTP is best considered a marker of couple fecundity for a population.[17, 44]

Adaptation of TTP

Several other innovative approaches to investigating infertility prevalence have been suggested. The 'current duration' approach uses a cross sectional survey design to record current durations of conception attempts. Using this design, couples who are currently engaged in unprotected intercourse are asked how long they have been exposed to possible conception without actually conceiving.[51-53] Such an approach is supposed to overcome some of the difficulties inherent in cohort designs, where the need to recruit a representative cohort can be problematic. The current duration approach is also able to include couples who have not yet conceived, whereas TTP studies are by nature limited to those who have successfully conceived.[51] However, it has been noted that current duration designs are only able to include TTPs that have not been censored before observation.[45]

An approach based on the 'case-cohort' design has also been suggested.[54] Olsen and Anderson explain that this approach is based on two stages of data collection. Firstly, a survey is performed (using random sampling) among women of reproductive age who are planning a pregnancy at time point t_0. This survey is used to collect data on the actual waiting time distribution among all women trying to conceive. Secondly, a

further prospective study collects information on reported TTP for all planned pregnancies beginning during a specified time period, starting at time point t_0 and ending at time point t_1. Clearly, some of the women included in the first survey will go on to conceive during the specified interval and will thus be included in both samples. The idea with this approach is that data on TTP is collected for all pregnant women in a defined region, while the first survey can provide information on the waiting time distribution for the underlying cohort of women.[54]

Impact of fertility treatment on definitions

The problem of defining infertility has been compounded by the development of assisted reproductive technology (ART) and other infertility treatments over the last few decades. This has enabled many women (and couples) to have children that they may have otherwise been unable to have. The situation is therefore confused: a couple who are only able to conceive with the help of treatment may still be infertile in the classic sense but no longer have unresolved infertility. Care must be taken when asking women to self-report TTP, as women may use a different starting point when pregnancies have been conceived through the use of ART and other treatment for fertility problems, leading to an inaccurately short TTP. It is also possible that the growing popularity of fertility treatment may mask other trends, for example, pregnancies conceived in this way may compensate to a degree for the natural decline in fecundity with increasing female age. It is also important to note that the use of fertility treatment is not evenly distributed[40]; in particular, ART use is commonly associated with certain socioeconomic characteristics where personal financial cost is involved. For all these reasons, pregnancies conceived through ART, and possibly other fertility treatments too, should ideally be considered separately from spontaneously conceived pregnancies.[40] Clearly, information about how a birth is conceived may not be available in many studies, particularly those that rely on routine data.

Historical approaches

In view of the difficulty in measuring infertility in contemporary populations, some studies have used historical data to assess the effect of specific exposures on female infertility. For example, the relationship between fecundability and season of birth was examined using a sample of women who married in the Netherlands between 1802 and

1929. The information from various civil and parish registries was used to derive 'family reconstitutions', and TTP was estimated as the period between marriage and estimated conception of first birth.[24] A similar approach was used by the same authors in subsequent studies.[23, 55] The limitations of such an approach include the assumption that marriage represents the commencement of exposure to unprotected intercourse. Also, such an approach looks at births only, and a long TTP may mask recurrent conceptions ending in an adverse outcome.

3.1.3 Comparing definitions in practice

Most research studies looking at infertility prevalence concentrate on one definition only. However, a number of studies have explored the use of multiple definitions, highlighting the varying estimates of infertility obtained using different approaches.

Data from an Australian case-control study on ovarian cancer in 2003[56] provides estimates of infertility prevalence according to three different measures: self reported difficulty in conceiving in combination with having consulted a doctor for this purpose; self-reported failure to conceive for a period of 12 months or more; and failure to conceive for a period of 12 months or more computed from reproductive histories created using information provided by women on contraceptive practices, sexual activity, and periods of pregnancy and lactation. Sixteen percent of the sample self-reported having had difficulties conceiving for which they consulted a doctor, and 23% and 20% for the self-reported and calendar definition of time-based failure to conceive respectively. Attempts to validate self-reported information on the proportion of women who had consulted medical services proved unreliable; only 23% of women who self-reported problems had this information confirmed by medical records. The authors overall conclusion is that self-reported difficulty conceiving is a useful measure of infertility, but the strengths and limitations of such an approach need to be taken into consideration.[56]

One US study compared five different definitions of infertility, applied to controls in the Cancer and Steroid Hormone Study.[57] All five measures concentrated on the absence of conception as the outcome of interest. Three measures were self reported (no conception after two years of trying to conceive; no conception after two years trying to conceive

and couple consulted doctor; no conception after two years and doctor diagnosed problem in woman, partner, or both), and two were computed from reported reproductive histories (no conception after 12 months of unprotected intercourse; no conception after 24 months of unprotected intercourse). The lowest prevalence of infertility was obtained using the proportion of women who reported having failed to conceive after two years in conjunction with a diagnosis (age adjusted prevalence 6.1%), the highest prevalence was the number who had been exposed to unprotected intercourse for a period of at least 12 months without conception (age adjusted prevalence 32.6%). The authors found that social class and ethnicity influenced prevalence according to the definition used, with a higher proportion of women with lower achieved education level and black ethnicity classified as infertile according to both measures of infertility computed from reproductive histories. The consistency of results does suggest that these groups had a higher prevalence of infertility.[57]

The majority of research on infertility has been carried in out in developed country settings. However, one particularly interesting study compared definitions of infertility in a survey carried out in Northern Tanzania. In this research, six different indicators of infertility were used. The first three measures were based on self-reports about waiting time to conception, ever having problems getting pregnant and unprotected intercourse for at least two years without conception. The third definition was consistent with the WHO definition based on failed attempts to conceive for at least two years. A further three measures of infertility were based on computed birth and marriage histories: no birth for at least five years subsequent to last birth or marriage; no birth for at least five years subsequent to last birth and marriage and confirmation that woman wants a/another child; and childlessness within marriage (whether woman has ever had a child, by specified duration of marriage). The results showed that the definition of infertility affected prevalence estimates more for secondary infertility (range 4.8-11.1%) than primary infertility (range 1.8-3.5%). The authors of this study concluded that estimates of infertility depend on whether a woman/couple perceive themselves as actively trying to conceive. This was based on results which found a higher number of women reporting unprotected intercourse for >2 years without a pregnancy than those who reported unsuccessfully trying to conceive for >2 years. The recommendation from

this study is that future studies use the WHO definition of "tried to conceive for at least 2 years".[25]

An interesting experiment was conducted by Sallmen and colleagues,[38] who used a hypothetical reference population to estimate the bias involved in measuring couple fertility using different study designs. This stimulation exercise involved keeping the fecundability distribution stable, but varying two parameters (the number of at-risk cycles where pregnancy may have unintentionally occurred; the probability that an unintended pregnancy continued to birth). Variation of these parameters over time was estimated using data from developed countries. They compared two study designs. The first of these was time to pregnancy among first pregnancy planners. The second used primary infertility as the end point, with those conceiving within a year classed as fertile, and those who were unsuccessful for a minimum of a year classed as infertile (even if they subsequently conceived). Their results suggest that TTP studies can be biased towards reporting an increase in fecundability over recent decades. However, in the contrasting study design using infertility rates, there was bias towards underestimating infertility in the past, suggesting a decrease over time.[38]

3.1.4 Conclusion: definitions

In recent years there has been particular attention paid to clarifying the terminology used within infertility research. A number of authors have proposed solutions to the current confusion.

In a recent editorial Habbema argued that "terminology in medicine should be lucid, understandable, consistent, and unambiguous". He proposed that that terms 'infertility', 'subfertility', and 'fecundity' be abandoned in favour of a new classification system. Under this alternative system he suggests that all couples experiencing fertility problems should be investigated and classified according to three dimensions: descriptive (length of primary/secondary non-conception); diagnostic (any problems, or unknown); and prognostic (from grade 0 almost normal fertility to grade 4 sterility).[11]

The uniform application of the term 'infertility' certainly is misleading, as is the way in which it is used interchangeably with 'subfertility'.[11] Some authors have suggested that

the term 'subfertility' is preferable to 'infertility', as it better conceptualises that many couples experiencing problems will eventually conceive.[58]

Whether or not researchers begin to adapt new terminology remains to be seen. It is clear however that the vast majority of existing literature is characterised by unclear and overlapping definitions of infertility. Whilst undertaking the literature review for this thesis, the terms used to refer to the reviewed primary studies are those used by the authors themselves. Where the authors do not clarify the terms under use, the term 'infertility' is used in its broadest sense to describe impaired fertility.

3.2 TRENDS AND PREVALENCE

3.2.1 Demographic trends

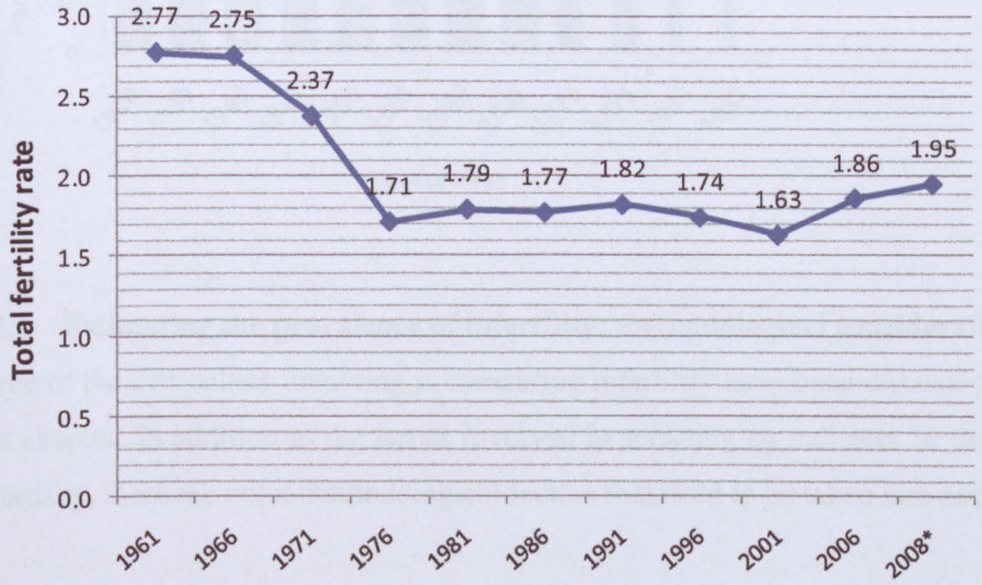
Discussions about the prevalence of infertility need to be considered in the context of wider demographic trends. In classic demography, the level of fertility in a non-contracepting population is primarily influenced by three factors: age at first union (marriage/partnership), prevalence and duration of breastfeeding, and level of mortality.[59] Given that the average number of children per marriage in 18th century Europe was 5-6 children, changes in the these trends (reduction in mortality, slightly older age at first union, limited breastfeeding) suggest that the number of children per marriage should have increased to nearer 10.[59] However the 'demographic transition' (move from high birth and mortality rates to low birth and mortality rates) has been accompanied by a move from natural to controlled fertility, attributable to the widespread use of contraception.

3.2.2 UK trends: national data

The UK and other developed countries have witnessed a steady increase in maternal age at first birth and subsequent births. Over the last few decades in the UK the average maternal age at birth has risen from 26.6 in 1971 to 29.3 in 2007.[60] Changes in average family size over time can be most accurately described by using the total fertility rate (TFR), defined as the average number of live children that a group of women would have if they experienced the age-specific fertility rates of the calendar year in question throughout their childbearing years. Patterns in data show that family size has decreased

in the UK and other developed countries over the last half century, with the total fertility rate lower than two in most European countries.[61] In the UK, data for 1961 to 2008 (Figure 3.1) shows a steady decline in TFR between 1960-1976, following which a period of near stability has given way to a slight increase since 2001.

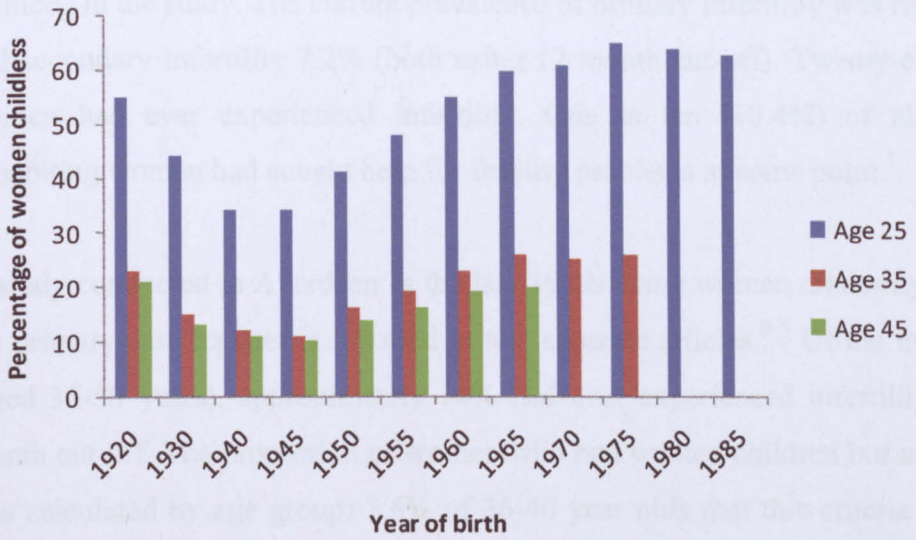
Figure 3.1: Total Fertility Rate 1961-2008 [60]



*2008 data based on projection

Routine data confirms a growing trend for women to remain childless at the end of their reproductive years. Figure 3.2 shows this trend, with the proportion of women childless at all ages lowest for women born in 1945, and a steady rise for birth cohorts born since then. However, there is evidence to suggest that this trend may be stabilising, or possibly slowly reversing, for the most recent birth cohorts. It is worth noting that these data do not differentiate between voluntary and involuntary childlessness, and it is this limitation which makes it necessary to look beyond routine data in order to accurately estimate the prevalence of infertility in the UK.

Figure 3.2: Childless women by age, by year of birth [60]



3.2.3 Estimating the prevalence of infertility: methodological considerations

Some of the difficulties involving in measuring infertility have been discussed earlier in this chapter. In addition to the issues involved in selecting an indicator or definition of infertility, there are other methodological factors that need to be taken into account.

The prevalence of infertility can be defined as the total number of women or couples who experience infertility within a given period of time and in a given place, in proportion to the total population in the same time and place.[62] In order to accurately estimate prevalence, ideally studies should utilise population-based samples. This is because of the difficulty in extrapolating prevalence from self-selected samples. The choice of population 'at risk' (the denominator) is as important as the numerator. Possible methods to ascertain infertility include self-report, clinical reports, and deduction from birth/reproductive histories.

3.2.4 UK population-based estimates

There have been few population-based studies carried out in the UK which report on infertility prevalence. Those that have been carried out tend to be small and limited in terms of representativeness.

Page conducted a small questionnaire survey in the 1980s using a random sample of women from a primary care practice list. [7] Only women aged 20-44 were eligible to be included in the study. The current prevalence of primary infertility was reported as 5.9% and secondary infertility 7.2% (both using 12 month cut-off). Twenty-eight percent of women had ever experienced infertility. One in ten (10.4%) of all married and cohabiting women had sought help for fertility problems at some point.[7]

A study conducted in Aberdeen in the late 1980s using women randomly selected from the primary care register is reported in two separate articles.[4-5] Of the included women (aged 36-50 years), approximately 14% had ever experienced infertility using the 24 month cut-off. The proportion of women who had wanted children but never conceived was calculated by age group: 2.6% of 36-40 year olds met this criteria for unresolved primary infertility, and 3.5% of 46-50 year olds. Other results from this study suggest that younger women were considerably more likely to seek help: 95.1% of women aged 36-40 with primary infertility had sought help compared with 72.1% of women aged 46-50. The authors also report that younger women seeking advice were more likely to be referred to hospital compared to older women who sought advice.[5]

Buckett and Bentick report information collected from another study based on women randomly selected from a primary care register in Shropshire during the 1990s.[8] Of the women aged 45-54 who responded to the survey, 17.3% and 12.0% reported ever experiencing infertility according to the 12 and 24 month cut-off respectively. Just over two percent (2.4%) had unresolved primary infertility – had not conceived at all despite repeated attempts. Nearly five percent (4.7%) had tried but not succeeding in achieving a live birth, this figure included women who had had one or more conceptions that ended in fetal deaths. Of all women experiencing problems with infertility, half (48.4%) sought medical help.[8]

Gunnell and Ewings carried out a postal survey in the mid 1990s using a random sample drawn from a health services authority register in Somerset.[6] The study sample consisted of women aged between 36 and 50 years old. Survey data were used to estimate the prevalence of infertility, both resolved and unresolved. Overall, 16.1% and 15.8% reported current primary and secondary infertility respectively using the one year

threshold. One quarter (24.4%) of women reported ever experiencing infertility (primary or infertility) defined as the inability to conceive for a period of 12 months or more, and 12.9% using the 24 month cut-off. Two percent of women had failed to ever conceive despite trying, and 3% had failed to have a live birth despite attempts. Of those with primary infertility, 50% had sought help from their GP and 30% were referred to hospital. The equivalent percentages for those with secondary infertility were 34% and 19%. As with the Aberdeen study, there was a trend for younger age cohorts to consult their GP more frequently and to be more likely to be referred for specialist help, although this trend was not significant.[6]

The most recent UK study looking at infertility prevalence was conducted in Aberdeen, Scotland by Bhattacharya and colleagues.[3] Uniquely, this study was conducted in the same region (the Grampian, Scotland) as the earlier study conducted by Templeton and colleagues.[4-5] The population in this area is reasonably stable, enabling comparisons between the two studies. Information was collected by postal questionnaire from a random population-based sample of women aged 31-50 years. One in five women met the criteria for infertility, defined as problems trying to conceive and/or help-seeking for fertility problems. Overall, at some point in their lifetime 17.5% of women had tried unsuccessfully to conceive for 12 months or more and 9.1% had tried unsuccessfully to conceive for 24 months or more. In terms of unresolved infertility 4.0% of all women had tried to get pregnant but had never conceived, with a similar prevalence when the focus was only on women aged 46-50. The majority of women with fertility problems had sought help: 68.7% and 73.0% of women with primary and secondary infertility respectively. A slightly higher proportion of women aged 36-40 had sought help compared to women aged 46-50 (73.6% vs. 67.1%). Despite these differences in help seeking behaviour, there was no significant trend across age groups of differences in prevalence of infertility when based on duration trying.[3] Bhattacharya and colleagues themselves compare the results of their study to the earlier one conducted by Templeton and colleagues[4-5] and report that overall the results of the two studies are similar with comparable estimates of infertility prevalence and help-seeking behaviour.

The studies reported above show fairly consistent results, and are in agreement with figures derived from reviews of studies carried out in many other countries,[31, 63] discussed below.

Four UK studies which have also attempted to estimate infertility prevalence are not included in the discussion above.[64-67] This is because they are not true population-based studies. All three of these studies selected a sampling frame and then used clinical data to provide the numerator. In the first study,[64] the numerator was derived from the number of couples referred to a specific infertility service, and in the latter three,[65-67] the numerator was defined as the number of patients at a general practice who had presented with fertility problems. Attempts to estimate prevalence in this way is problematic. The number of cases is often inaccurate, as it is reliant on there being no bias in measuring and recording the outcome.

3.2.5 International estimates

Two high quality reviews have attempted to report on estimates of infertility prevalence derived from a wide range of international studies.[31, 63]

Schmidt and Münster reviewed 22 epidemiological studies conducted in industrialised countries (Europe, Australia and the US) and published between 1970-1992.[63] They report that the current prevalence of infertility among women during fertile years varies from 3.6-14.3%, and lifetime prevalence varies from 12.5-32.6%. Data from the studies included in their review give a range of involuntary infecundity (defined by the authors as no live birth despite trying, not specifically measured at the end of the childbearing period) between 2.6-5.0%; consistent with the UK data reported above. The overall proportion of women who have sought medical help for fertility problems ranged between 3.6-17%; among those experiencing primary or secondary infertility the percentage range as reported is 32-95% and 22-79% respectively.[63]

A more recent review published by Boivon and colleagues in 2007 considered population surveys carried out since 1990 in any country.[31] In addition to providing estimates of infertility prevalence, the authors also aimed to quantify the potential need for infertility care worldwide. Reviewed studies covered a wide range of populations

and settings, with some surveys focusing only on older women, and other surveys sampling women across the reproductive age span. Lifetime prevalence of infertility ranged from 6.6-26.4%. Prevalence of current infertility ranged from 3.5-16.7% with a median estimate of 9% for women of reproductive age and infertility defined as a conception delay of 12 months or more. These figures apply to data collected in developed countries. The equivalent data for less developed countries (for which there is considerably fewer data) suggest that despite a different range, the median estimate for these countries is also 9%. In terms of care-seeking, the review suggests that 42-76.3% of couples in developed countries and 27-74.1% of couples in less developed countries seek care. Overall, the authors estimate that 45% of couples who experience fertility problems do not seek care (range 30-60%). The authors conclude that both prevalence and demand are very similar between more and less developed countries. They suggest that on the basis of current world population, an estimated 72.4 million couples are currently infertile and approximately 40.5 million are currently seeking help for fertility problems.

3.2.6 Declining fertility?

There has been some suggestion that human fertility has declined in recent decades. This question is particularly difficult to investigate, not least because of the plurality of social and economic factors that may affect choices about childbearing, requiring us to look beyond purely descriptive analyses conducted using routine data. As discussed earlier, there has been a strong trend towards delayed childbearing in most developed countries including the UK; controlling for this confounding effect of age presents a significant methodological challenge. There is also the need to account for the increasing use of infertility treatment which may mask increasing subfertility. Furthermore, it is impossible to not take into account male fertility when considering whether fertility has declined over recent decades. There has been some evidence of a decline in semen quality according to studies carried out in UK and other European countries, but the evidence is by no means consistent.[68] Other issues that may affect infertility prevalence over time include the risk of sexual transmitted infection[69] and other medical conditions that affect fertility.

To minimise possible bias and confounding in studies that attempt to investigate changing infertility prevalence, it has been suggested that studies are conducted using homogeneous population subgroups where birth control is prohibited. However, such populations are highly self-selected and any results are unlikely to be generalisable to the general population.

As discussed earlier, two population-based prevalence studies were conducted in the same area of Scotland, UK nearly 20 years apart (1988 and 2007). [3-5] When the results of these two studies were compared, the overall results in terms of estimates of infertility prevalence and reported help-seeking behaviour were similar. The exception to this was infertility assessed using the threshold of 24 months, with infertility prevalence slightly lower among women aged 46-50 in 2007 compared to women aged 46-50 in 1998. The authors of the later study speculate that this might be due to changing trends in the utilisation of medical investigations and treatment, with a more proactive approach in recent years. On balance it appears that the evidence is not strong enough to suggest a decrease in infertility over time. A comparison of the results of these two studies certainly reveals no evidence to support an increase in infertility.[3]

An analysis of Swedish medical birth registry data attempted to consider whether the prevalence of subfertility has changed over time. Information on subfertility was collected from pregnant women, who were classified as subfertile if they had experienced a period of more than one year during which they did not become pregnant.[70] The authors compared age-specific proportions of subfertile women, by birth cohort (5 year groupings, <1949 to >1970). The results suggest that subfertility actually decreased in Sweden during the study period, from 12.7% in 1983 to 8.3% in 1993. For primiparous women aged 25-29, 17% born in 1950-54 reported subfertility compared to 6% born in 1965-1969.[70] The authors hypothesise that this observed decrease in subfertility is attributable to eradication of gonorrhoea (which reduced prevalence of secondary subfertility).[70]

Another Swedish study, this time a cross-sectional survey, compared women born between 1936-45 to women born between 1946-60. The results of this study suggested that fecundability (measured as the probability of conception) did not differ between

these two birth cohorts. It is worth noting however that there was no age-standardisation involved in this comparison, although the data were restricted to women who gave birth below the age of 29.[71] Similarly, no decrease in fecundity by increasing year of birth was observed in a Danish study which compared twins born between 1931-1952 who had completed their childbearing.[72]

One UK cross-sectional population-based survey asked both men and women about TTP and found that recent conceptions tended to occur slightly earlier than those in previous decades. These findings were in opposition to the study hypothesis, which expected to find delayed conception more likely in recent pregnancies. This trend was consistent regardless of whether respondent was male or female and after discounting possible bias as minimal, the authors state that it provides evidence of rise in couple fertility.[68]

In contrast, a study conducted in the US using population-based data provides some evidence of a decline in fecundity over the period 1982-1995. Based on a series of nationwide surveys, the authors report that the proportion of women aged 15-44 who reported fertility problems rose from 8% in 1982 to 10% to 1995.[33]

Studies which look at trends in help-seeking for fertility problems and attempt to extrapolate findings to the real prevalence in infertility are likely to be affected by bias. As discussed earlier, there is evidence that help-seeking behaviour is associated with socioeconomic status and other factors which are likely to change over time. A number of studies have also identified a trend for help-seeking behaviour to differ by birth cohort, with more recently born women seeking treatment more frequently and/or at an earlier point.[6, 73] As one highly distinguished author suggests "couples have become increasingly impatient over the last 20 years, accepting failure and delayed conception less and less willingly".[12]

3.3 INFERTILITY SUBTYPES

A detailed consideration of the clinical subtypes of infertility is beyond the scope of this thesis, but some background context is necessary. Infertility can be categorised according to whether problems are found in the female partner, male partner, both or

neither. It is estimated that in 30% of couples infertility is predominantly attributable to the male, in 54% of cases attributable to the female, and in 25% of cases infertility remains unexplained after investigation. These percentages do not add up to 100% because it is estimated that as many as 15% of couples will have more than one cause for their infertility.[74]

The three most common medical causes of subfertility are sperm dysfunction, ovulation disorders, and tubal factor problems. Accordingly, the UK clinical guidelines suggest that in couples reporting fertility problems, both partners should be investigated. Semen analysis and assessment of ovulatory function are the recommended first stage investigations, with tubal occulation tests recommended subsequently.[28]

Sperm defects or dysfunction – primarily reduced motility, normality and survival - are associated with approximately 30% of couple infertility.[64] The complete absence of sperm is very rare, representing less than two percent of cases referred to specialist fertility clinics.[74] Semen analysis is one of the most straightforward of infertility investigations, with diagnosis preferably only taking place after multiple semen analyses and in accordance with established criteria such as those produced by the WHO. It is also worth noting that even where serious sperm defects or dysfunction are present, female fertility can compensate for male subfertility, and therefore results of semen analysis may be a poor predictor of future couple fertility.[75]

Ovulatory disorders are the most common cause of infertility in women, estimated to contribute to 25-30% of all couple infertility.[13, 64, 76-77] Ovulation disorders can be diagnosed by performing blood tests, however, it has been said that the only absolute proof of normal ovulation is pregnancy.[13] The WHO classifies ovulatory disorders into three sub-types. The first, hypothalmic pituitary failure, is responsible for approximately 10% of all ovulatory disorder infertility.[15] This diagnosis may be triggered by excessive exercise and/or extremes of weight.[77] The second type, hypothalamic pituitary dysfunction, is the most common, affecting around 85% of women with ovulatory disorder.[15] Polycystic ovarian syndrome falls into this category, accounting for approximately 70% of ovulatory disorder infertility.[77] Lastly, ovulatory disorders can also be attributable to ovarian failure, affecting around five percent of women with

ovulatory disorder infertility.[15] Cases of polycystic ovary syndrome (PCOS) and hypothalamic-pituary causes may respond to ovulation induction treatment. The outlook for other causes of ovulation failure such as premature ovarian failure and genetic abnormalities are generally less positive.

Approximately 11-30% of couple infertility is attributable to tuboperintoneal factors.[13] Tubal damage may be caused by infection such as chlamydia or gonorrhoea, by pregnancy sepsis, intrauterine devices (IUDs), or it may result from post-surgery complication.[78] Adhesions in the tubal cavity may be severe enough to cause obstruction. Chlamydia is the major cause of pelvic inflammatory disease (PID), and is often implicated in cases of tubal infertility. Chlamydia serology is a recommended investigation for women reporting infertility problems.[74] There is also evidence to suggest termination of pregnancy may cause pelvic infection resulting in infertility.[79] In severe cases, endometriosis can cause tubal damage with resulting detrimental effect on infertility.[80] It is estimated that approximately five percent of infertility problems in women can be attributable to endometriosis.[28]

Mild endometriosis without clear tubal damage has also been implicated in female infertility. The mechanism by which endometriosis without tubal involvement may affect fertility is unclear,[81] because of this it is generally recommended that mild or moderate endometriosis is considered under the umbrella heading 'unexplained infertility' and managed accordingly.[28]

Uterine abnormalities are diagnosed in around 10-15% of women seeking help for infertility problems. This includes fibroids, estimated to occur in up to 30% of women with a detrimental though unclear effect on fertility suggested in a minority of cases (estimated to be 10%).[80] Other causes of infertility include sperm-cervical mucus interaction. It is estimated that cervical hostility may be a major cause of infertility in 9-15% of couples.[13]

In 15-30% of couples who undergo fertility investigations no clear diagnosis can be made.[13, 64, 74, 76, 80, 82] This diagnosis of 'unexplained' infertility is considered to be a diagnosis of exclusion, only made in cases where routine investigations have revealed

no abnormalities – i.e. the presence of normal sperm parameters, normal ovulation, tubal patency and a normal uterine cavity.[80] It has been suggested that unexplained infertility represents the single most frequent female infertility diagnosis.[81]

The tendency to diagnose unexplained infertility reflects the lack of sensitivity in many tests that are used during fertility investigations. Clinicians are able to establish whether any tuboperitoneal damage is visible, but there is no way to assess the transport of eggs and sperm through tubes.[80] It has been proposed that unexplained infertility should be re-termed undiagnosed infertility, due to the difficulties involved in diagnosing causes of infertility and the likelihood that there may causal factors implicated that have yet to be identified.[81]

3.4 DETERMINANTS OF INFERTILITY

In this section the determinants of infertility are reviewed. A plethora of determinants have been investigated, ranging from more straightforward sociodemographic and lifestyle factors to more intricate examinations of the interplay between intergenerational and early life exposures. A number of reviews on the determinants of female infertility, male infertility, and infertility in general have previously been published,[83-91] highlighting in many cases conflicting evidence regarding the role of different factors.

Relevant primary research reports and reviews were identified through thorough searching on Medline (OvidSP) using a combination of free-text terms and MeSH headings. Searching using free text terms was also conducted using Google Scholar. References and citations were checked for particularly relevant review articles. Highly relevant journals (Human Reproduction, Fertility and Sterility, BJOG, Human Fertility) were also hand-searched.

In women, the determinants of fertility are commonly explored using studies that collect information on TTP. This indicator of infertility is generally considered to be preferential to measures of help-seeking behaviour, known to be particularly prone to bias. Before embarking on a discussion of determinants, it is important to re-emphasise the difficulty in distinguishing infertility from early fetal loss. Recurrent early

subclinical fetal loss may manifest as conception delay, with the causes of fetal loss potentially different to infertility defined as an inability to conceive. In addition, it must be remembered that TTP is a marker of couple fertility and it is often difficult to disentangle exposures experienced by female and male partners.

Although the focus is primarily on risk factors for infertility in women, the role of exposures on male fertility is also briefly discussed. Studies evaluating effects on male fertility tend to take one of two approaches: they either look at semen quality as a proxy measure of male fertility; or they assess conception delay, measured as TTP (a marker of couple fertility). It has to be emphasised that sperm parameters do not necessarily reflect male fecundability.

3.4.1 Infection

Genital tract infections have been hypothesised as a possible cause of both male and female infertility. The focus has generally been on female infertility, in part because of the higher number of processes involved in the female reproductive system. However, when looking at the role of sexually transmitted infections it is important to note that infection is often shared. Ideally, studies looking at the role of infection on delayed conception should adjust for the infection status of the other partner.

In women, fallopian tubes are particularly vulnerable to infection and damage,[78] and pelvic infection is considered a major cause of tubal subfertility.[78] PID, a bacterial infection of the upper genital tract, can result from ascending cervical infections.[92] PID is not a particularly specific or sensitive diagnosis, but adhesions attributed to this diagnosis are considered to be implicated in tubal factor infertility.

Of all the potential infections, infections caused by chlamydia trachomatis are the most common sexually transmitted infections (STI) worldwide.[93] The exact link between chlamydial infection and infertility is unclear, with one recent systematic review concluding an absence of valid evidence on the burden of tubal factor infertility attributable to genital chlamydial infection.[94] However, a well designed systematic review carried out more recently suggests that the risk of tubal infertility after lower genital tract chlamydial infection ranges between 0.1-6%. This figure can be further

broken down to a risk of PID after chlamydial genital tract infection of 1-30%, and a risk of tubal infertility after PID of 10-20%.[92] Infection with gonorrhoea has also been linked with PID and a subsequent higher risk of tubal factor infertility.[78]

Previous use of an intrauterine device (IUD) has been linked with infertility, but a recent review concluded that there is little reliable evidence that IUD use is associated with either PID or reduced fertility. It is has been hypothesised that IUDs are associated only with infection immediately after insertion, resulting in a temporary increased risk which reduces to a level comparable with non-IUD users shortly afterwards.[78] In fact, studies show that women who discontinue IUD use have normal prospects of pregnancy and a normal distribution of pregnancy outcomes.[95]

A number of studies have suggested that bacterial and viral infections of the genital tract may be significant causes of male infertility. It has been hypothesised that infections could be implicated in the following factors: deterioration of spermatogenesis; impairment of sperm function; and obstruction of the seminal tract.[96] The link between chlamydia and semen quality is equivocal, with no firm evidence supporting a link.[93] It has also been suggested that male accessory gland infection (MAGI) may have negative effects on male fertility undetectable by routine semen analysis. According to this theory, semen parameters may appear normal, but on further investigation adverse effects on the functional capacity of spermatozoa may be apparent.[97] Overall, a recent review has concluded that there is not yet strong and consistent evidence to support a causal link between infections and male infertility.[96]

3.4.2 Sociodemographic factors

Age

Age is probably the most well known predictor of female infertility and has also been shown to be associated with infertility in men, though the relationship between age and infertility in men seems to be less consistent. A recent European survey of couples practicing natural family planning found that increased infertility in older couples is primarily attributable to reduced fecundability not absolute sterility. In other words, the decline in fertility with both male and female age appears gradual.[98]

In women, the number and quality of oocytes is known to decline with age, with the resulting decline in fecundity becoming clinically relevant by the mid 30s.[99] It has been suggested that the effect of aging on oocyte quality is the most 'striking' cause of declining fecundity, evidenced by the higher rate of early fetal loss observed in older women.[99]

Female age at conception is often reported to be a significant predictor of TTP.[100] One study carried out in the Netherlands found that for each increasing year of female age, the overall live birth rate decreased by 2%.[101] Another possible explanation for infertility increasing with age in women is that exposure to infections may result in tubal infertility, and the cumulative risk of exposure to infection clearly increases with age. This hypothesis is supported by studies which suggest that age is associated with subtype of infertility. Data from a Scottish fertility clinic found that compared to younger women, women over 35 were more likely to have a either a diagnosis of tubal factor infertility or unexplained infertility.[102]

Endometriosis and fibroids, both implicated in some cases of infertility, are also more common with increasing age.[103-104] Decreased frequency of intercourse may also go some way to explain lower fecundability among older women. Body mass index (BMI), parity, contraception, education and social class are all factors associated with age and possibly fertility.

It is difficult to ascertain the independent effect of age on fertility due to the preponderance of potential confounding factors. In order to minimise the role of bias and confounding in elucidating the effect of female age on fecundability, researchers have taken innovative approaches, including the study of historical populations practicing natural fertility. One such study found a gradual linear rise in sterility until age 40, then a more rapid increase in sterility from 40 onwards among 16-19th century English parish dwellers.[105] Contemporary studies have examined populations of women undergoing ART as a result of male factor infertility in attempt to negate the effect of male age and patterns of coital activity. One study focused on women undergoing

artificial insemination by donor (AID), confirming a slight decrease in fecundability from 30 onwards, more marked from 35.[106]

It has been suggested that ART and other widely available treatments for fertility problems may lull women into a false sense of security regarding their ability to conceive.[103] However, it has been argued that infertility treatment alone cannot compensate for the loss of fecundability caused by delayed attempts to conceive.[99] Even if pregnancy is achieved, increased age is associated with a higher risk of adverse outcomes, including miscarriage, ectopic pregnancy, multiple births and chromosomal abnormalities.[107-109] One prospective linkage study carried out in Denmark found that the proportion of pregnancies ending in fetal loss (miscarriage, stillbirth and ectopic pregnancy) rose from 9% at 20-24 to 75% in women aged 45 or more.[107] The increased risk of miscarriage with advancing female age is likely to be attributable to a combination of factors, including a higher risk of chromosomally abnormal pregnancies as well as decreasing uterine and hormonal function. It is important to remember that as outcomes, miscarriage and infertility are inextricably linked; a delay in conception described as subfertility may be a result of recurrent early (and thus undetected) miscarriage.

It is also important to highlight that that the question of the association between female age and infertility is complicated by a birth cohort effect on the likelihood of seeking treatment for infertility. An observed increase in infertility, if measured as an increase in the proportion of women or couples seeking help for problems conceiving, may partly be an artefact. Women in younger age cohorts are more likely to seek help for infertility; and may do so after a shorter period of non-conception.[6, 73]

Age has also been implicated as being associated with fertility in men. As with women, isolating the effect of age on male infertility is difficult due to potential confounding. For example, male sexual dysfunction, known to be associated with age, can sometimes be behind a couple's reported infertility problems.[110] Female age is also highly correlated with male age, with 60% of marriages in 2001 occurring to partners with an age gap of four years or less and a similar trend observed throughout the 20th century.[111]

Some studies have reported an effect of male age on the likelihood of conception,[98, 112-113] a finding observed in nine of the 11 studies included in a relevant review.[114] The authors of this review report that the association between increased male age and delayed conception persisted after adjustment for the effect of female age in those studies that took account of such potential confounding.[114] There is also some evidence that in women undergoing AID, decreased pregnancy rates are associated with increased age of donor.[115]

Evidence supporting an association between age and semen parameters is equivocal. A review conducted in 2001 found that older age was associated with decreased semen volume, sperm motility and sperm morphology, but not with sperm density.[114] Two studies utilising the same sample of US men with no history of infertility support the findings of a decrease in the number of motile sperm and decreased semen volume with increasing age.[116-117] An increase in the number of morphologically defective sperm with older age has been reported in other studies,[116-119] as has the finding that semen volume decreases with age.[110, 116, 118, 120] However, the finding that sperm density is lower in older men has not been consistently confirmed, although the results of one large study suggested a decrease in sperm concentration with increasing age.[121] Several recent studies have found that sperm DNA damage is also associated with age,[120, 122] although this is a relatively new area of investigation and the implications are still unknown. Overall, although the evidence suggests an effect of male age on most semen parameters, it seems that this represents a gradual decline rather than the stronger threshold effect observed in women.[117]

Socioeconomic status

Socioeconomic status is unlikely to be a determinant of infertility *per se*, but it has been hypothesised to be associated with the reporting of fertility problems and/or the seeking of medical help. Few studies have investigated the role of socioeconomic status, and those that have report inconsistent findings. Any observed association between fertility problems and socioeconomic status is likely to be confounded by factors such as sexual behaviour, BMI and lifestyle behaviours such as smoking and alcohol consumption, also known to impact on fertility. In addition, the availability and cost of fertility treatment is likely to affect the number and characteristics of those who seek treatment.

In one Swedish cross-sectional survey primary infertility in women was associated with a higher level of education.[71] However, a number of studies have reported opposing findings. In a series of population-based surveys conducted in the US, the probability of 12 month infertility was higher in women without a college degree.[33] A study conducted in Sweden using registry data looked at the proportion of pregnant women reporting subfertility; those with a greater number of years of education were significantly less likely to report subfertility compared to those with less than nine years of education.[70] One Danish study looked at the association between multiple socioeconomic measures and infertility. The authors report that only education was possibly associated with infertility, with women without a college education more likely to exhibit primary subfecundity.[123] One UK study based on retrospective recall of TTP reported that area-based social deprivation (measured by the Index of Multiple Deprivation) was associated with longer TTP, an association that remained after adjustment for potential confounding.[124]

A UK survey found that rates of infertility did not vary by occupational group, but an association with the seeking of treatment for infertility was found, with women from professional occupational groups more likely to seek treatment.[6] A similar finding was reported in a Finnish study, where treatment was more frequently accessed by urban, highly educated, and affluent women.[125]

Two recently published UK studies provide further evidence about the relationship between socioeconomic indicators and infertility reported by women. One analysis conducted by myself and colleagues found that both higher socioeconomic status and achieved education were associated with increased reporting of fertility problems. However, these factors were not associated with help-seeking, nor the likelihood of having received fertility treatment.[34] Another study addressing this issue was conducted using survey data collected in the North East of Scotland, and reported no significant associations between the number of women reporting infertility and any of the measured socioeconomic indicators: social deprivation, education status, partner's employment status, own or partners' occupation.[3]

Studies looking at infertility in women often use indicators of socioeconomic status of her male partner. However, there is very little information on the role of socioeconomic status on indicators of male fertility. As studies of semen parameters are often conducted using self-selected samples of men already being investigated for fertility problems, it is hard to remove the bias caused by differential help-seeking behaviour. In addition, there is evidence that men who participate in semen analysis studies differ from those who do not,[126] with one study finding that lower educational status was more common among non-participants.[127] Nevertheless, one study has reported that there was no difference in occupational level among men with low and normal sperm counts.[128] In a small case-control study conducted in Singapore, men from technical, managerial and professional occupational groups were at greater risk of infertility compared to service and clerical workers.[129]

3.4.3 Body size

Body size, usually measured using BMI, is reported to be associated with fertility problems in both men and women.

There is fairly consistent evidence that BMI in women is associated with infertility. Repeatedly, research studies have demonstrated an association between both underweight and low BMI, and obesity/high BMI, and infertility.[3, 83, 124, 130-132] One US study focused on ovulatory infertility and found a U-shaped association with BMI.[133]

After taking into account menstrual abnormalities, women with high BMI are more likely to experience delayed conception.[134-135] Extremes of BMI in women are associated with decreased pregnancy rates among those undergoing *in vitro* fertilisation (IVF),[136] with one studying quantifying this as a 33% reduction in the live birth rate for women with a BMI>27 completing their first cycle of IVF.[101]

Obesity is associated with metabolic disturbances, and it is modulation of insulin sensitivity and resulting disruption to ovarian function that is thought to be partly responsible for negative effects on fecundity.[137] PCOS, characterised by hyperandrogenism and oligo- or anovulation (and discussed in more detail later in this chapter), is the most common cause of anovulation and ovulatory disorder infertility.[138]

Obesity is more common among women with PCOS, though not universally observed.[139] The evidence suggests that obesity both exacerbates symptoms in women already diagnosed with PCOS, and also possibly triggers the development of PCOS in susceptible populations.[140] Therefore, some research has concluded an interaction between obesity and infertility mediated by PCOS.[141]

The hypothesis that the effect of obesity on fertility is partly mediated by ovulatory problems is supported by studies that show ovulation induction is less effective in obese women[142-143] and those that demonstrate a longer TTP among obese women.[137] The effect of obesity on infertility thought to be small but significant. However, the fact that obesity is also associated with increased TTP suggests that the observed association between BMI and infertility is not purely attributable to anovulation and/or PCOS.[137, 144]

Underweight women have also been found to also be at an increased risk of subfecundity. Normal calorie intake and a certain level of body fat are necessary for onset of puberty and regular ovulation.[141] This is thought to due to a mechanism which protects severely malnourished women from the high energy costs incurred through pregnancy and lactation. Low body weight is an established cause of amenorrhoea. At least one study has confirmed a link between weight loss/leanness and subfertility, thought to be mediated through reduced estradiol levels and suspension of ovulation.[133]

The effect of body size on male fertility has also been investigated by several studies. One Norwegian retrospective cohort study reported a trend of increased subfertility with increased male BMI, where subfertility was defined as conception delay of at least 12 months or having received fertility treatment.[145] The relationship between body size and semen parameters has also been considered. A large Danish cross-sectional study reported that both high and low BMI was associated with reduced semen quality, namely sperm count and sperm density. However, sperm motility was not associated with BMI.[146] Several recent reviews provide further evidence that male obesity may have a negative effect on a number of semen parameters.[147-148]

3.4.4 Lifestyle/behavioural factors

Alcohol

The evidence for an association between alcohol consumption and infertility is inconsistent.[141] Most studies have not found any association between moderate or light drinking and subfecundity in women or men,[3, 42, 149-150] but a negative effect of heavy alcohol consumption on fecundity in both sexes has commonly been reported.[124, 151]

A Danish study prospectively following couples trying to conceive found that the highest probability of conceiving within six months was observed in women consuming less than five drinks per week compared to those consuming five or more.[150] Another Scandinavian prospective study found that women with higher alcohol consumption were more likely to experience medical examinations for infertility.[152] Curiously, one population-based prospective study found that alcohol consumption measured at baseline was only associated with infertility among women over 30, not in those under 30.[153]

At least one study has reported a link between moderate drinking and infertility in women, particularly where infertility is attributable to ovulatory disorders or endometriosis.[154] However, other studies have not provided evidence to support the hypothesis that alcohol consumption is associated with impaired ovulatory fertility.[44]

One study looked at the consumption of specific types of alcohol among women using data from the Danish National Birth Cohort. Results suggested that wine drinkers had shorter TTP than non-wine drinkers. There was no association between beer drinking and TTP, and the relationship between spirit drinking was unclear due to small numbers. It is plausible that these results suggest characteristics of wine drinkers are responsible rather than the wine itself.[155]

Chronic high-level alcohol use is known to affect semen quality, with studies investigating semen parameters in alcoholics reported reductions in volume, total sperm count, density and the number of morphologically normal sperm.[156] There is little evidence of an effect of light or moderate alcohol consumption on semen parameters,[120, 129, 157-159] although the findings of at least one study suggest that alcohol and cigarette

consumption may interact to produce an adverse effect on semen quality that is not apparent when these factors are considered independently.[157]

Smoking

There is compelling evidence that cigarette smoking has a negative impact on female fertility. Findings from a number of studies also suggest that smoking has a negative effect on male fertility, although the association is controversial and not consistently supported by all the evidence.

A meta-analysis synthesising the literature on smoking and infertility in women has confirmed a higher risk of infertility in smokers compared to non-smokers.[160] Although the effect size reported in this systematic review was not large, a consistent effect was observed across all included studies despite differences in methodology and strategies to control for confounding. Several subsequent studies and a further review have added to this weight of evidence.[124, 161-163] At least one study has suggested an association between passive smoking and delayed conception as reported by women.[161]

Evidence suggests that cigarette smoking has a negative effect on every system involved in the female reproductive process.[164] Despite the fact that such research has been ongoing for more than two decades; the mechanism(s) for an effect of smoking on fertility are not clearly understood. Animal studies have provided some evidence that nicotine has a negative effect on ovulation.[163] Evidence from human studies have also reported evidence that has a negative effect on ovarian follicle maturation[141] and appears to accelerate follicular depletion.[164] A review of relevant studies provides evidence of cigarette smoking being consistently associated with a slightly earlier menopause, suggesting overall that the risk of menopause in women aged 44-55 is twice as high for smokers compared to non-smokers.[165]

It has also been suggested that smoking could affect tubal or cervical function, either indirectly or directly. The effect of smoking on tubal infertility seems to be particularly strong[83] and there is some evidence that risk of ectopic pregnancy is increased in smokers.[166] Tobacco appears to have negative effect on uterine receptiveness, although the literature to support this association is limited.[164, 167] There is also a possible effect

of cigarette smoking on oocyte pick up, movement down the fallopian tube, fertilisation and early embryo development.[141]

Cigarette smoking in women appears to negatively affect success of ART,[151] with lower rate of successful clinical outcomes observed among smokers undergoing IVF (success measured by IVF cycle).[101, 160, 168-169] One study that looked specifically at ovarian stimulation and oocyte retrieval found that such procedures were associated with lower success rates among smokers[170]; this finding was supported by a review which confirmed a negative effect of smoking on the effectiveness of ovarian hyperstimulation, oocyte quality and development, and overall clinical outcomes.[164]

Heavy smoking in men also appears to be independently associated with delayed conception in spontaneously conceived pregnancies.[42, 124, 161] At least one study has found that male smoking decreases the success rate (measured as clinical pregnancies) of both IVF and intracytoplasmic sperm injection (ICSI),[171] although a review which focussed primarily on female smoking noted an inconsistent effect of male smoking on clinical pregnancy rates.[169] There is evidence that smoking has a negative effect on semen parameters, with a number of studies reporting decreases in sperm density, sperm count and the number of motile sperm.[87, 129, 172] The finding of decreased sperm density observed in smokers was confirmed by a well designed meta analysis, however it was noted that this effect was strongest in 'healthy' men (i.e. not those sampled from clinic attenders).[173] Other studies have however found that smoking has no significant independent effect on semen parameters,[120, 157, 174] although one of these studies noted that an effect was observed when men who consumed alcohol in addition to smoking were compared to men who neither smoked nor consumed alcohol.[157] Also, it is important to emphasise that even if an effect of smoking on semen parameters is observed, this does not always translate to impaired fertility.[173]

Physical activity/exercise

The evidence on the relationship between physical activity and infertility is less clear, and few relevant studies have been conducted. A particular challenge for relevant studies is the need to isolate the effect of physical activity on fertility from potential confounding by body size. For example, women who report particularly high levels of

physical activity are also more likely to be underweight, which is in itself an independent risk factor for ovulatory infertility.

One large study conducted in the US suggested that vigorous physical activity may protect ovarian function, independent of the effect of BMI.[133] However, this association was not significant for moderate activity. Conversely, one Norwegian study found an increased risk of infertility was found for the small number of women reporting highest levels of physical activity.[175] Physical activity may be associated with hormone profile and may affect fertility via this mechanism, possibly increasing insulin sensitivity. Exercise is also linked to socioeconomic status and mental health, both of which may confound any association between physical activity and fertility. Nevertheless, some studies have reported finding no association between levels of physical exercise and reported infertility, as in a population-based study conducted recently in Scotland.[3]

The relationship between physical activity and male fertility is even more poorly understood. One small study found no evidence of physical activity on semen quality.[159] Some studies have investigated semen parameters in men who are involved in regular and vigorous physical activity (for example athletes), but it is debatable how far such results are generalisable to the general population.

Caffeine consumption

Some studies have investigated the effect of caffeine consumption on fertility in men and women, though in general the findings are largely inconsistent.

There is some evidence of an association between caffeine consumption in women (especially high consumption) and infertility. Delayed conception has been found to be associated with caffeine intake in women in a number of retrospective studies[176-177] and at least one prospective study.[178]

Some studies have found an effect only when looking at heavy consumption: seven or more cups a day were associated with subfecundity but not TTP among fertile women in a UK survey,[124] and one large multicentre found only large amounts of caffeine (>500 mg/day) were associated with delayed conception.[176]

One large well designed prospective study did not find any association with total caffeine consumption and ovulatory disorder infertility; where a slight increase in soft drink consumption was associated with decreased fertility, this was considered to not be attributable to the caffeine content in such drinks.[44] A retrospective study carried out in Canada also did not provide any evidence that caffeine consumption, even at high doses, was associated with TTP.[42]

The possible mechanisms by which caffeine may affect female fertility are largely unclear, though it is worth noting that one study has found that high levels of caffeine intake tend to be associated with infertility due to tubal disease or endometriosis.[179]

Very little is known about the effect of caffeine on male fertility, and those studies that have investigated this relationship generally report inconsistent results. One study looked at TTP and found that heavy tea drinking in men was associated with subfertility, but no such effect was observed for coffee drinking.[42] A recent Danish study found no evidence for an association between moderate caffeine consumption and decreased sperm quality. However, those who consumed high quantities of caffeine-based cola drinks were more likely to have lower sperm quality. The authors conclude that this association is unlikely to be attributable to caffeine, as similar results were not observed for other caffeine-based drinks.[180]

Recreational drug use

Investing the effect of recreational drug use on reproductive outcomes is difficult due to ethical considerations and under-reporting of exposure[90] and few studies have looked at the specific effect of recreational drug use on fertility, particularly female fertility.

One small case-control study conducted in the US attempted to look at recreational drug use and female fertility.[181] The findings of this study suggest that women who with a history of smoking marijuana have increased risk of infertility due to ovulatory problems, especially where there had been recent use. This finding is apparently supported by the results of animal studies.[181] Cocaine use was associated with tubal infertility; the authors hypothesise this may be explained by a higher risk of sexually

transmitted infection.[181] Despite the findings of this study supporting an effect of drug use on fertility problems, the evidence is sparse. The authors of one Australian study report that recreational drug use in women had an insignificant effect on time to conception in their analysis.[124]

In one small study of male partners in couples seeking help for fertility problems, marijuana use was not associated with differences in total sperm count or sperm motility.[182] Another study found some suggestion of an effect of cocaine use on semen parameters: long term cocaine use was more common in men with low numbers of motile sperm and low sperm density.[183]

Micronutrients

The effect of nutritional status on fertility, particularly in terms of the role of specific micronutrients, is a relatively recent area of investigation. There is some suggestion that iron, folate and zinc may all be associated with specific reproductive processes in women, but the evidence is very limited.[84, 184] Male infertility has been investigated in a slightly larger number of studies, but overall the evidence is still weak. Both zinc and folate have been linked to parameters of semen quality,[185-187] as has antioxidant intake.[188]

Stress

Measures of psychological stress are heavily correlated with fertility problems, but the independent effect of stress in infertility is particularly difficult to investigate because of possible reverse causation: stress can be a result of infertility as well as being considered a potential cause. There is strong and consistent evidence that experiencing problems trying to conceive leads to stress, and a considerable weight of evidence supports the stressful nature of undergoing fertility treatment.[189-190]

One observational study conducted in Denmark followed couples trying to conceive and reported a lower conception rate per cycle for women who reported the most stress.[191] There is also some suggestion that psychological stress and/or anxiety in women has a negative affect on the success of IVF and other outcomes in women undergoing ART.[192-193]

A number of studies have attempted to investigate the effect of stress on measures of semen quality, reporting mixed results. One early study of couples undergoing IVF reported that sperm samples collected during IVF treatment cycles were lower quality than those collected before treatment.[194] The findings of one US study of healthy volunteers found no effect of job-related stress of life event stress on semen quality. However, in this study a small effect of specific stress - recent family bereavement – was observed as having a negative effect on semen quality.[195] Data from a Danish prospective study following couples trying to get pregnant reported no effect of stress (measured using the General Health Questionnaire) on semen quality,[196] but a recent US study reported that two or more stressful life events were linked to poorer semen quality.[197] At least one study has reported that depression in men is possibly associated with semen parameters.[198]

3.4.5 Occupational and environmental exposures

A number of occupational and environmental exposures have been identified as risk factors for infertility, although in general the focus has been on male fertility. Studies of occupational and environmental hazards to female infertility are predominantly small and many report inconsistent results. TTP is the most commonly used outcome measure in studies of this kind. Several reviews of the link between environmental pollutants and fertility have previously been published.[88-89, 151, 199-204]

Occupational exposures can be separated into those attributable to a physical factor and those where chemical agents are responsible for any hypothesised effect on fertility. One study looked at TTP and occupational risk factors in women such as working hours, shift work, and use of visual display units (VDUs). The authors reported no independent effect of any of these factors on TTP.[177] Another UK study provides some evidence of an association between exposure to low level ionising radiation and primary infertility in women.[205]

In terms of chemical agents, evidence has been reported for an association between impaired female fertility and chemicals used in dry cleaning and printing industries, solvents, nitrous oxide and inorganic mercury.[151, 199] There is some suggestion that specific chemicals e.g. the synthetic pesticide dichlorodiphenyltrichloroethane (DDT)

may be implicated in precocious puberty,[141] with possible consequences for adult fertility. In addition, there is the well known case of exposure to diethylstilboestrol (DES), which has been associated with reduced fertility in women, and increased rates of ectopic pregnancy, spontaneous abortion, and preterm birth.[199, 206] Women who live or work in agricultural settings seem to be at increased risk of infertility, possibly attributable to exposure to certain herbicides and/or fungicides.[207]

A plurality of studies have looked at the effect of male exposure to occupational and environmental factors and possible effects on male fertility, and many of these primary studies have been included in comprehensive reviews.[203-204, 208-211]

Exposures in men that have been linked to reduced fertility (measured as TTP or other indicators of subfertility, such as help-seeking for fertility problems) or changes in semen quality include occupational lead exposure,[88, 212-213] radiation,[88, 214] organic solvents,[215-216] occupational heat exposure,[217-218] and pesticides. [88, 204, 216, 219] The evidence is rarely consistent however, and other studies have found no evidence to support an effect of male infertility on the following exposures: occupationally related categories of magnetic field exposure,[220] solvents,[214] occupational lead exposure,[199, 214] extremely low frequency (ELF) magnetic fields,[221] low level ionising radiation,[205] and pesticides.[214, 222-223]

One factor that is often discussed in relation to male infertility is genital heat stress. In order to promote normal testicular function, a temperature between 2-4 °C is required,[218] and increased scrotal temperature is frequently postulated as having a deleterious effect on semen quality.[224-225] Scrotal heating may be attributable to endogenous factors such as varicocele and cryptorchidism. It is also hypothesised to result from exogenous factors activities such as hot baths, laptop use, and tight fitting underwear; men with fertility problems or those trying to conceive are commonly warned off these activities. The evidence supporting this hypothesis tends to come from small studies, and reviews emphasise the need for further research in this area.[224-225]

3.4.6 Early life factors

An increasing body of evidence supports association between *in utero* or early exposures on health and other outcomes in adulthood. The literature has given rise to the suggestion that early life factors may also be associated with reproductive outcomes in adulthood.

Early life factors and fertility in women

A growing body of evidence has investigated links between early life factors and reproductive outcomes later in life, including timing of menarche and menopause, the development of specific conditions known to be associated with fertility (e.g. PCOS and endometriosis), and infertility in more general terms.

Few studies have directly examined the relationship between early life and *in utero* factors and fertility in adulthood. This is partly attributable to the difficulty in accessing good quality prospective data. Studies based on birth cohort designs are rare and expensive. It is also worth noting that the ability to investigate adult outcomes among those born very low birthweight and/or very preterm is conditioned by survival, with improvements in survival over the last few decades only now facilitating the collection of reliable data on outcomes in adulthood.

Markers of *in utero* growth and fertility

A brief analysis of Swedish data from the birth cohort analysed in this thesis (Chapter 5) found no association between preterm or low weight for gestational age and childlessness in adult women.[226] A more detailed analysis of this dataset looked at social and biological determinants of 'reproductive success' – defined as the total number of children and grandchildren born.[227] Results of these analyses suggest an association between certain social and biological factors and reproductive success measured in this way. Among women, a higher birthweight for gestational age, a term birth, a younger mother, and a higher birth order were all associated with a greater number of descendents. The authors suggest that the detected associations are partly mediated by the probability of marriage. This was considered to be particularly important for the observed association between birthweight for gestational age, which

appeared to have little association with reproductive success when the analysis was restricted to only those married.[227]

Several other studies have reported finding an association between *in utero* factors and fertility, although the direction of the association is not always as hypothesised. A study using Danish national birth cohort data looked at the effect of self reported birthweight and gestation on fecundability. The results suggest that both women who reported a low birthweight or high birthweight were at increased risk of experiencing a TTP of one year or more. The authors report that the effect of low birthweight was strongest in those with a BMI <25 in adulthood, while the effect of higher birthweight strongest in those with a BMI or 25 or more. These results are surprising, as it refuted the authors' hypothesis that low birthweight in conjunction with high BMI would lead to a longer TTP.[228] A study using Swedish registry data found a reduced probability of giving birth among women born very low birthweight. Interestingly women born small for gestational age appeared more likely to given birth. These inconsistent results may be a result of bias resulting from the censoring of women at age 27 due to limited follow-up.[229] Clearer results were found in a study using Norwegian registry data. Women who were born preterm had a lower probability of overall reproduction (defined as a livebirth/stillbirth), with the reproduction rate appearing to directly increase with increasing gestation at birth up to a levelling off at 35 weeks.[230] A large US study looking at a range of adult outcomes in those born very low birthweight found lower rates of pregnancy and livebirth in this sample compared to those with a normal birthweight.[231]

One recent study used data from a French community-based cohort of young adults to look at the relationship between being born small for gestational age (SGA) and fertility. The authors report that there was no difference in either reported TTP or the adjusted fecundability ratio (estimated as the monthly probability of conception) between women born SGA (<10^{th} centile) and those born appropriate for gestational age (AGA) (weight between the 25^{th} and 75^{th} centile).[232]

Several studies have investigated fertility in populations exposed to causes of restricted growth *in utero*, using this as a proxy for fetal growth restriction. Of particular note are

a number of studies which investigated subsequent fertility in women exposed *in utero* to the Dutch famine of 1944/45.[233-234] Women were traced in adulthood, and those who were exposed (*in utero* during the famine period) compared to those born shortly before, or conceived after (unexposed). One of these studies found no differences between exposed and unexposed women regarding any of the following outcomes: age at menarche, the proportion ever married, age at first marriage, the proportion having no children, age at first child and inter-delivery interval. The only significant finding was an excess of perinatal death among offspring of famine-exposed women. The authors comment that overall these findings are reassuring and do not support the hypothesis that acute caloric restriction *in utero* impairs female fertility.[233] The second study reported surprising results; exposed women seemed to report more successful fertility. They had significantly more children, were younger when they had their first child, and less frequently childless. The authors discuss possible explanations for these results, but after closer examination of the data find no evidence for the possible role of genes or biological fitness to reproduce.[234] A third study suggested that severe famine exposure during childhood (as opposed to *in utero)* decreased the likelihood of both first and second birth. There was also evidence that the risk of medical infertility and surgical menopause was increased in those who were exposed to famine in childhood. Overall, the authors suggest their findings provide evidence for moderate impairment of reproductive function.[22]

Markers of *in utero* growth and timing of menarche

Any effect of *in utero* factors on fertility in adulthood may be mediated by timing of menarche, an association investigated by a number of studies. In one analysis of British birth cohort data, initial analyses suggested that higher birthweight was associated with a later onset of menarche. However, once growth in infancy was taken into account, the reverse was true, i.e. those heavier at birth had an earlier menarche onset. The authors of this study suggest that growth in infancy and childhood may mediate the relationship between *in utero* environment and timing of menarche.[235] A large survey in the Philippines looked at various measures of *in utero* growth in relation to timing of menarche.[236] The results of this study suggest that longness and thinness was associated with earlier menarche, but there was no evidence that birthweight *per se* was associated with timing of menarche. The association between thinness at birth and earlier

menarche was strongest in those who had a higher than average rate of growth in the first six months of infancy. The authors of this study conclude that birthweight and SGA are not independently associated with age of menarche; faster growth in infancy appeared to predict early menarche.[236] One Swedish study reported that girls born SGA reached menarche on average of five months earlier than girls who had a normal birthweight for gestational age. This study found no evidence for an effect of prematurity on age at menarche.[237]

The relationship between timing of menarche and adult fertility is also unclear, with no consistent association observed. In some studies, earlier menarche has been associated with indicators of a diminished ovarian reserve.[238] One US population-based study found no difference between reported age at menarche and total number of pregnancies, although women with 'extreme' age at menarche (<12 or over 15) were less likely to ever have a livebirth. The proportion of adverse reproductive events (stillbirths, induced abortions, infertility) under study did not vary with age at menarche, except for ectopic pregnancy which seemed to be associated with age at menarche. Age at marriage and age at first pregnancy was also related to age at menarche.[239] One Japanese survey reported a higher mean age at menarche in those diagnosed with infertility, but this finding was primarily attributable to a higher risk of infertility in those who reported a very late menarche (18 or older).[240] No overall association was found between recalled menarche and infertility in a cross sectional study in Denmark. However, early menarche (<11) was associated with both a higher risk of PID and spontaneous abortion. The authors suggest that this finding may be attributable to 'early coital debut'.[241] Spontaneous abortion is known to be associated with infertility, and a higher risk of spontaneous abortion was observed among women who reached menarche before 12 in a Norwegian study.[242]

Markers of *in utero* growth and timing of menopause

The key determinant of timing of menopause is the number of ovarian follicles retained at birth.[243] The number of follicles peaks around five months gestation, with loss occurring as early as the start of the postnatal period. It has been hypothesised that one of the ways in which suboptimal growth *in utero* may affect fertility is through a detrimental effect on the development of these follicles or through increasing early loss.

Several studies have found no association between birthweight or gestation and age at menopause.[243-245] However, one recent analysis of 1958 British birth cohort data reported a U-shaped association between birthweight and menopause by 44-45 after adjustment for confounding factors. The same study found that birthweight standardised by gestational age was also associated with age at menopause, although this association was only true for women with the highest birthweight standardised for gestational age, who were more likely to reach menopause by 44-45. Gestation was not associated with age at menopause in this study, suggesting that it is growth rate rather than early gestation that may be associated with reproductive ability.[246] In addition, an earlier study conducted using a smaller UK sample found that both shorter length at birth and higher ponderal index were associated with earlier menopause.[244]

Possible mechanisms

Any discussion of the possible interplay between *in utero* factors and fertility needs to take into account the growing literature on possible mechanisms that underlie such associations. This includes discussion of the relationship between early life factors and development of the reproductive organs, and also a specific consideration of the role of PCOS.

A number of studies have looked at markers of fertility in those born small for gestational age and/or low birthweight. These studies have reported a catalogue of associations between markers of restricted growth and reproductive outcomes such as precocious pubarche, earlier menarche, reduced rate of ovulation in adolescence, smaller uterine size and decreased ovarian volume.[247-251] The observation that menarche occurs approximately 5-10 months earlier in those born SGA has been supported by studies of girls with precocious pubarche but also those with early-normal onset of puberty.[250] Ovarian development has noted to be impaired in severely growth restricted fetuses.[252] The suggested mechanism behind these findings is insulin resistance resulting in endocrine modulation *in utero*, with growing evidence that girls born low birthweight are more likely to be hyperinsulinemic.[247, 250] The long term impact on fertility of findings that *in utero* growth is associated with reproductive characteristics in childhood and adolescence is as yet unknown.

Any discussion of the relationship between early life or pubertal factors and fertility also needs to take into account the possible role of PCOS. The fact that PCOS is the most common cause of anovulation in women[77] means the link with infertility is indisputable. Between 4-8% of the general female population are thought to have PCOS,[140, 253] thought the method for diagnosing this condition remains contentious.[140] PCOS appears to be a heritable disorder with evidence of familial clustering.[254-255] However, there is no clear consensus as to the exact genetic basis,[139] although it is generally agreed that it represents a complex multigenic disorder.[256] An adverse intrauterine environment has been implicated in the development of PCOS.[256] Whether this is attributable to restricted growth *in utero* or more specific exposure *in utero* (e.g. to excess androgens) is unclear.[257] Both women who are born low birthweight and those who experience premature pubarche appear to be particularly susceptible to early menarche and development of PCOS in adolescence.[258] However, at least one study has reported no association between PCOS and birthweight.[259] Other studies have reported that women with PCOS tend to be older at menarche than those women without PCOS.[139, 238]

Effects of other *in utero* and intergenerational exposures

There has also been a growing interest in the effect of other *in utero* exposures on fertility. Animal studies support a hypothetical association between maternal smoking in pregnancy and fecundity of daughters. Human studies evaluating indicators of fertility have in general reported inconsistent findings.[260-262] One recent Norwegian study which analysed data from a large cohort study reported a small effect with *in utero* exposure to tobacco associated with a slightly longer TTP in daughters. [263] Another recent study reported that maternal smoking was associated with reduced uterine size in adolescence, but no association was observed between smoking *in utero* and reduced ovarian volume or markers of ovarian reserve.[264]

Some attempts have been made to look at the relationship between fertility and intergenerational factors, going back further than the *in utero* phase. A study based on family reconstitutions among women born in late 19th and early 20th century in The Netherlands reported on decreased fecundity observed among daughters of older mothers. The suggestion is that an effect of maternal age on reproductive ability may be

traced a generation back.[55] The evidence in favour of an intergenerational effect of birthweight is reasonably strong, with one large Swedish study using birth registry data reporting that women born SGA have a higher risk of giving birth to infants who are also SGA [265] and a similar study using women from the Danish Population Register reporting that women born SGA were twice as likely to give birth to a SGA infant compared to women born not SGA.[266] Similarly, data from one Scottish retrospective cohort study found that women born to mothers who had at least one spontaneous preterm delivery were more likely themselves to have a spontaneous preterm delivery.[267]

Early life factors and infertility in men

The process of spermatogenesis is only initiated in puberty, and for this reason research into factors that affect male fertility have tended to concentrate on adult exposures. However, the mechanism by which spermatogenesis is triggered develops *in utero*, and there has been growing interest in prenatal exposures for this reason.

The evidence regarding an association between early life and *in utero* growth and male infertility is inconsistent. One study of couples receiving care for fertility problems reported that men with unexplained infertility (abnormal semen analysis but no clear etiology) had a lower mean birthweight compared to both men with normal semen analysis and men with explained infertility. On the basis of these findings the authors suggest that reduced fetal growth is associated with unexplained male subfertility.[268] Another study has suggested that being born small for gestational age is a risk factor for reduced testicular size.[269] However, two subsequent studies conducted in different populations did not replicate these findings. In a Danish study, no strong associations between semen parameters and either birthweight or ponderal index were observed.[270] In a case-control study carried out in Aberdeen, the authors reported that neither the mean birthweight nor the proportion low birthweight differed between men with unexplained infertility (cases) and those men with normal semen analysis (controls).[271]

Despite the lack of evidence regarding an effect of perinatal factors on infertility *per se*, data do support the hypothesis that fetal growth restriction is associated with increased risk of specific male reproductive health problems, including hypospadias and

cryptorchidism, and possibly also testicular cancer.[272] These three conditions also appear to be risk factors for impaired sperm quality in adulthood. It has been suggested that testicular cancer represents the most extreme manifestation of a syndrome of disordered reproductive development.[208] Following on from this idea, the theory of *testicular dysgenesis syndrome* (TDS) has been proposed, whereby cryptorchidism, hypospadias, low sperm quality and testicular cancer are considered to be a group of outcomes which share a common etiology.[273-275] It is hypothesised that this syndrome may result from adverse *in utero* environmental exposure.[273] There is little evidence of endocrine disrupting factors affect semen quality in humans, though animal studies do support such a link.[275] The theory of TDS has been rejected by some authors, who point out the both the lack of epidemiological evidence confirming non-causal associations between the different outcomes and the paucity of evidence supporting the idea of a shared etiology.[272]

The case for a possible effect of *in utero* factors on male fertility is supported by studies which show an association between particular *in utero* exposures and fertility. A factor commonly investigated by such studies is maternal smoking, which has been shown to be negatively associated with semen parameters.[276] Some studies have also looked at the role of endocrine-disrupting agents, most notably *in utero* exposure to DES which is now known to have an adverse effect on male fertility.[277] There is also an issue regarding the heritability of male infertility, with some studies showing clustering of male fertility problems in families [278-279] and some evidence that men whose mothers received ART have poorer semen quality in adulthood.[280]

3.5 INFERTILITY AND REPRODUCTION

In recent years there has been increasing interest in the clustering of adverse reproductive outcomes. It has long been established that experiencing an adverse outcome such as fetal death, low birthweight or preterm birth is associated with increased risk of the same outcome in subsequent pregnancies.[281-282] Increasingly the context has been widened by investigations of how different adverse reproductive outcomes may be linked and experienced by the same woman. Central to this discussion is the notion of 'reproductive frailty', that is, the tendency of women to be predisposed

to multiple adverse reproductive outcomes. The clustering of adverse outcomes with subfecundity has also been termed 'key reproductive disorder'.[283]

This section of the thesis contains a consideration of different adverse reproductive outcomes, reviewing the evidence regarding how these events tend to cluster together. The discussion will concentrate on infertility measured in various ways, as it the consideration of this outcome which is most pertinent to this thesis.

3.5.1 Defining adverse reproductive outcomes

Earlier in this thesis a comprehensive discussion of the difficulties involved in defining infertility was provided. It is important to emphasise again the need to take into account whether pregnancies result from infertility treatment or whether they were spontaneously conceived. Most studies that look at infertility in relation to other adverse outcomes concentrate on spontaneously conceived pregnancies, however some do not. This is important because there is evidence to suggest that treatment itself may be independently associated with adverse perinatal outcomes,[284-287] though it is notoriously difficult to separate the effect of treatment from any effect of infertility *per se* or differing obstetric management of treatment-related pregnancies.

Infertility is not the only outcome that is difficult to define; defining other reproductive outcomes presents similar issues of confusion and complexity. Attempts to clearly define such outcomes are necessary before a detailed discussion of their relationship with infertility.

Termination of pregnancy (TOP), also known as induced abortion, or more simply just shortened to 'abortion' in everyday language, refers to the ending of pregnancy through removal or induced expulsion of the products of conception (embryo/fetus, placenta etc.).

Clearly, TOP differs from other adverse outcomes in that women may choose to have a termination. The vast majority of terminations carried out are considered 'elective' (sometimes referred to as 'social'), whilst a minority are described as 'therapeutic' or 'medical' and clinically indicated due to a problem with the pregnancy or fetus. In

clinically indicated cases where there is a problem with the pregnancy and/or fetus, TOP may pre-empt a likely spontaneous abortion. Similarly, a proportion of elective TOPs would have ended in a spontaneous abortion if they had not been terminated.

The process by which a TOP is carried out depends on gestational age. In early terminations (first trimester), the approach is medical or surgical. Medical terminations require no surgical intervention and are carried out with the aid of pharmaceutical drugs. Surgical terminations are most commonly carried out using vacuum aspiration. Second trimester terminations are rare and considerably more complicated; in some cases these are carried out by induction of labour in conjunction with an injection that ensures the fetus is not born alive. Difference in abortion method is important because some commentators have suggested that any association between TOP and subsequent subfertility or other problems may be attributable to an increased risk of infection or mechanical trauma resulting from invasive termination.[288]

It is worth noting here the suggestion that a history of TOP may be a predictor of high fertility. This is due to the fact that accidental/unintentional pregnancy is associated with high fecundability,[40] and such pregnancies are statistically more likely to end in termination than 'intended' pregnancies.

Miscarriage

Miscarriage, also known as spontaneous abortion, can be defined as the spontaneous end of pregnancy occurring between early pregnancy and a defined point in mid pregnancy. The consensus generally is that a fetal death before the legal limit for defining a stillbirth is considered a miscarriage; this threshold is 24 weeks in the UK. Miscarriages are often categorised as 'early' or 'late' by stage of pregnancy (first trimester vs. second trimester) or by gestational age in weeks (commonly <12 completed weeks vs. ≥ 12 weeks, or <14 weeks vs. ≥14 weeks). Miscarriage is a common outcome in pregnancy, with overall estimates suggesting that as many as one in three pregnancies that survive the implantation stage result in miscarriage.[289-290] The risk of miscarriage decreases with gestation, resulting in lower prevalence estimates taken from self-report data as subclinical fetal loss is rarely included in these estimates.

The investigation of miscarriage as a reproductive outcome is complicated not just by the upper gestational threshold, but also by the difficulty in diagnosing fetal loss when it occurs early in pregnancy. Many miscarriages occur before pregnancy is clinically detected,[291] with estimates suggesting that as many as 50-60% of all conceptions are lost within first month of pregnancy.[290] With such under-reporting of miscarriage likely, it is no surprise that recurrent early miscarriage may contribute towards subfecundity (appearing as longer TTP); conversely, infertility may mask recurrent very early fetal loss. It is possible that there is differential misclassification, with certain groups of women more likely to detect early pregnancy loss. This has been implicated as particularly problematic in studies which compare the rate of fetal loss in women undergoing ART to women without fertility problems, because women undergoing ART are likely to be monitored closely and early pregnancy recognition may be a marker of risk itself.[40]

Stillbirth

Stillbirth is defined as fetal death after a defined point in mid-pregnancy. In the UK, this cut-off is 24 weeks, but this definition is not consistently applied throughout other industrialised countries. Most stillbirths occur at full term, that is at 37 weeks or later. Data on the incidence of stillbirths is well recorded in the UK and most developed countries due to the legal requirement to register such events. UK data show that the rate of stillbirths in 2008 was 5.1 per 1,000 births.[292]

Ectopic pregnancy

Sometimes referred to as an extrauterine pregnancy, an ectopic pregnancy is a complication of pregnancy whereby implantation occurs outside the uterus. The majority of ectopic pregnancies occur in the fallopian tubes, though exceptionally implantation occurs elsewhere, usually in the ovaries. Surgical intervention is often necessary, particularly where early diagnosis is missed. A common complication of ectopic pregnancies is that one fallopian tube needs to be removed. According to UK data for 1997-2005, approximately 11 per 1,000 pregnancies are ectopic.[293]

Other adverse reproductive outcomes

A number of other reproductive events are often included under the loose umbrella term 'adverse reproductive outcomes'. These include, but are not limited to, preterm delivery (usually defined as <37 weeks), small for gestational age (varying definitions) and low birthweight (<2500 grams). The latest available national data on gestational age suggests that in 2005 7.6% of all live births occurred at a gestation below 37 weeks (data for England and Wales only).[294] In 2007, 7.2% of all live births in England and Wales were low birthweight infants. [295] The prevalence of small for gestational age varies according to the threshold used, but one of the most commonly used measures classifies all birthweights below the 10th centile for gestation-specific birthweight as small for gestational age.

3.5.2 Infertility and prior adverse reproductive outcomes

Studies that directly look at secondary infertility and any association with prior reproductive outcomes are few and far between. One UK study looked at a range of adverse reproductive outcomes to see if they were predictors of later infertility. This study used various indicators of infertility: TTP, conception rates, and 'subfecundity' (defined as TTP >12 months). The results of this study suggest that TTP is prolonged after miscarriage, but not after stillbirth or ectopic pregnancy. Curiously, a longer TTP was observed after TOP compared to before TOP. However, when this was considered alongside TTP before and after livebirth, it appeared that this was explained by a higher than average fecundity before TOP and a reduction to average fecundity afterwards.[296]

A study comparing couples attending antenatal clinics in Manchester (UK) and Melbourne (Australia) found that in neither population was a history of induced abortion associated with subfecundity (defined as a conception delay of 12 months or more).[297] A registry based study in Finland attempted to investigate history of induced abortion among women being treated for infertility (IVF or ovulation induction). The authors reported that a considerable number of cases had a history of induced abortion, but when this was compared to age matched controls the difference was not significant.[298] A small Swedish study that compared women with tubal infertility to women without fertility problems found that similar proportions reported a history of induced abortion,[299] and a case-control study in the US which compared women with

tubal infertility to fertile women reported that a history of induced abortion did not appear to increase the risk of tubal infertility.[300] This latter study was also included alongside earlier studies in two reviews investigating the effect of induced abortion on a number of subsequent reproductive outcomes.[301-302] Both of these reviews concluded there was little evidence to support an association between induced abortion and secondary infertility.

A number of studies have found an association between infertility and a prior history of spontaneous abortion [297, 303-304]; one such study was able to look at subclinical fetal loss and found that women with fertility problems reported this outcome more frequently.[304] However, at least one study has reported finding no association between infertility and history of spontaneous abortion.[299]

Other studies have found associations between infertility and the following risk factors: preeclampsia,[305] prior caesarean section,[306-307] and the use of hormonal contraception.[308]

3.5.3 Infertility and subsequent reproductive outcomes

Several studies have considered the relationship between infertility and subsequent reproductive outcomes. Although not directly relevant to the analyses conducted in this thesis, synthesising the findings of such studies may help us to understand the causal pathways involved in the patterning of such outcomes.

A number of studies have provided evidence for an association between history of fertility problems and adverse reproductive outcomes in the current or future pregnancies. One UK survey of female radiographers found that those with primary or secondary infertility had an increased risk of fetal death in subsequent pregnancies.[309] An analysis of Australian data suggests an elevated risk of perinatal mortality in births occurring to infertile women compared to all births. This trend remained when subgroup analysis examined births that did not result from ART (i.e. untreated infertility), although the authors, and an editorial note, recommend caution due to possible bias.[310] However, the finding that the risk of perinatal death is higher among untreated infertile women was also reported in a subsequent UK study.[311] An analysis using data on primiparous women from the Danish national birth cohort found that the risk of

neonatal death increased with TTP; the highest risk observed for women reporting TTP of 12 months or more. Pregnancies were further classified into those resulting from ART and those not; non-ART related pregnancies to subfecund women seemed to be associated with the highest risk of neonatal death. No such association was observed for post-neonatal death.[312] In secondary analyses of three Swedish studies, pregnancies conceived after delayed conception (increased TTP) were associated with a higher risk of miscarriage (early and late) and ectopic pregnancy.[313] The risk of neonatal death was not found to be higher among pregnancies occurring to women with unexplained infertility compared to the general obstetric population in a study conducted in Scotland.[314]

Regarding other outcomes, a US cohort study which used conception delay as a marker of impaired fecundity did not find any association between impaired fecundity and birthweight or gestational age. It is worth noting however that by the authors' own admission the study involved a highly select sample, as only 15% of the eligible sample had a known TTP.[315] Another study focussing on pregnancies experienced by women with unexplained and untreated infertility found no difference in gestation, birthweight or the risk of congenital malformations when compared to women without fertility problems. However a small increase in breech birth was noted.[316] At least one study has noted an increased risk of preterm delivery in pregnancies with delayed conception.[313] and a study conducted in Finland using routine clinical data found that longer TTP was associated with less favourable obstetric outcomes in the current pregnancy, including gestational diabetes, placenta previa, and assisted delivery.[317] Similar results were reported by authors conducting an analysis of obstetric outcome in women with unexplained infertility, with a higher incidence of obstetric outcomes such as pre-eclampsia, preterm labour, and induction of labour occurring in infertile women compared to women in the general population.[314]

3.5.4 Clustering of other adverse reproductive outcomes

A considerable number of studies have attempted to ascertain how adverse outcomes other than infertility cluster together.

Generally it has been found that fetal death is strongly associated with other adverse outcomes. One large registry based study carried out in Denmark, looked at adverse perinatal events after spontaneous abortion. Compared to women whose first pregnancy ended in a live birth, those with a history of spontaneous abortion had a higher probability of preterm and very preterm birth.[318] In another study, an increased risk of preterm birth in subsequent pregnancies was only clear with a history of two or more miscarriages.[319] This study also confirmed an association between history of one or more stillbirths and subsequent preterm birth.[319] The evidence for an association between miscarriage and subsequent risk of low birthweight or intrauterine growth retardation is less clear. Both miscarriage and stillbirth have been found to be associated with low birthweight,[320] but in other studies authors have not found evidence to support this association.[318] Preterm delivery, SGA and perinatal mortality were all reported more frequently in a cohort with a history of recurrent miscarriage in a UK study conducted by Jivraj and colleagues.[321]

Findings relating to the role of induced abortion and subsequent outcomes are conflicting. One large European case-control study comparing preterm births to term births reported that a history of induced abortion was associated with risk of preterm birth. The association was strongest for very preterm birth, with a dose-response trend observed (risk of preterm birth increased with number of induced abortions). This study also looked at subtypes of preterm birth and found the clearest association was between induced abortion and spontaneous preterm birth.[322] Evidence for a general association between induced abortion and preterm birth has been provided by other studies[319, 323] and a number of reviews[301-302], although in one study the association was only significant when a history of two or more induced abortions was considered.[319] One small prospective study found no evidence of a significantly increased risk of preterm birth in women with prior induced abortion.[324]

The evidence for an association between induced abortion and low birthweight in a subsequent pregnancy is also unclear. Some studies report an association,[320, 325-326] while others conclude there is little evidence of effect.[324, 327]

A comprehensive systematic review and meta analysis of 37 studies investigating induced termination and subsequent outcomes reported that previous TOP is associated with a higher risk of low birthweight and preterm delivery. No consistent association between previous TOP and SGA was detected.[288]

Induced abortion has also been linked to miscarriage in subsequent pregnancies.[328] One study found that this association was only significant when two or more induced abortions were taken into account. The authors report that the association was not explained by the actual method of abortion.[329] However, the results of two reviews provide little evidence of an association between induced abortion and subsequent miscarriage.[301-302]

3.5.5 Conclusion

Overall, the evidence gives weight to the hypothesis that multiple adverse reproductive outcomes may cluster in the reproductive experience of a single woman. There seems to be consistent evidence that infertility and fetal loss, particularly miscarriage, are associated with each other, regardless of the timing of such events (whether infertility precedes or follows fetal loss). The evidence for an association between termination and future fertility problems is inconsistent.

3.6 NEXT STEPS

The following chapters describe analytical research on infertility using two large datasets: (i) a large historical birth cohort study based on infants born in Uppsala, Sweden between 1915-1929 (Uppsala Birth Cohort Study Multigen); and (ii) a more contemporary study based in the UK which aimed to construct the reproductive histories of a sample of UK women (The National Women's Health Study).

Chapter 4: Uppsala Birth Cohort Study Multigen - Data collection and methods

This chapter details the design, methods and analysis strategy for research conducted using the Uppsala Birth Cohort Study Multigenerational Study dataset (UBCoS Multigen). This dataset is based on the linkage of the obstetric records of all 12,168 infants born between 1915-1929 at the Uppsala Academic Hospital who survived to adulthood, and extensive information on this cohort and subsequent generations derived from routine sources including censuses, hospital discharge registers, cancer registries and the medical birth registry.

4.1 AIMS AND OBJECTIVES OF THE UBCOS ANALYSES

The aim of these analyses was to explore the hypothesis that *in utero* growth impacts on later fertility of women. The specific objectives were as follows:

- To describe the characteristics of this sample of women.
- To present and interpret general and age-specific fertility rates according to specific early life factors relating to *in utero* growth (preterm birth, low birthweight, small for gestational age status, and low ponderal index).
- To determine the effect of the above mentioned early life factors on estimated time to first birth among a sample of married women in the UBCoS cohort.

4.2 STUDY DESIGN AND POPULATION

4.2.1 Study design and setting

The Uppsala Birth Cohort Multigenerational Study (UBCoS Multigen) is an extension of the Uppsala Birth Cohort Study (UBCoS), a well established dataset based on the 14,611 births occurring between 1915-1929 at the Uppsala Academic Hospital in Sweden. Approximately 75% of births in Uppsala City and 50% of births in parishes less than 20km from Uppsala took place in the hospital during this period.[330] In establishing UBCoS, detailed obstetric data were extracted from hospital records and

double-entered into a computer program. Further details of the original data collection are described elsewhere.[330] Of the original 14,611 infants born, 6977 were female. Of these female infants, 6351 were liveborn singletons who were traced and survived to their first birthday.

Initially, those infants born during the study period (1915-1929, known as 'Generation 1' – 'G1') were traced through parish records. The system of personal identity numbers (introduced in Sweden in 1947) enabled the linkage of the obstetric data on these original UBCoS G1 members to other routine data sources. One of these is the Swedish Multigeneration Register, a register of approximately nine million people ('index persons') born after 1932 who have been resident in Sweden at any point since 1960.[331] The register contains information on biological parents of these index persons, and using this register, up to five generations of births have been traced to the 5854 G1 women alive and resident in Sweden in 1947. The linkage has been extended to include data sources such as national censuses, hospital discharge registers, cancer registries and the medical birth registry. One that is of particular relevance to the analyses reported here is the national censuses. Of the 6977 G1 female infants born, 5005 were linked to the 1960 census, enabling information on adult socioeconomic status and marital status to be linked to the G1 obstetric data and information on the number of biological children born to G1 women.

This large linked dataset was named UBCoS Multigen, and represents a unique and unrivalled resource enabling the investigation of intergenerational effects on health and social outcomes. Currently, UBCoS Multigen members have been followed up to 2002. UBCoS Multigen data have already been used for numerous pieces of research including those investigating social and early life effects on obesity, circulatory disease, cancer disease, reproductive success, mortality and health inequalities.[227, 332-338] A small piece of work looking at the relationship between early life factors and childlessness[226] provided the starting point for the research reported in this thesis. My own work on this topic begun in 2006 following a visit to the UBCoS Multigen coordinating centre at the Centre for Health Equity Studies (CHESS) at the University of Stockholm.

4.2.2 Data sources

The analysis described here focuses on G1 women and the number and timing of their biological children, drawing on data from three main sources. Obstetric and sociodemographic data were abstracted from the original G1 obstetric records collected as part of the original Uppsala Birth Cohort Study. The details of biological children (G2 children) born to G1 women were taken from the Multigeneration register. Data on civil status and adult socioeconomic circumstances of the G1 women was derived from the 1960 population census (the first census to be linked to UBCoS).

4.2.3 Sample size and study power

Sample size calculations were performed using the *stpower cox* function in Stata 10 (Stata Corporation, College Station, TX USA) reflecting the main analyses which used Cox regression to investigate time to first live birth. Birthweight for gestational age (classified as a binary variable – small for gestational age vs. appropriate for gestational age) was taken as the primary exposure. Calculations assumed a statistical power of 0.80 and an alpha (significance) value of 0.05 using a two-tailed test. Table 4.1 shows the different sample sizes necessary for hazard ratios ranging from 0.10 to 0.90. According to these figures, the ability to detect a hazard ratio of 0.7 requires a sample size of 247 pregnancies in each group. Taking into account that the proportion exposed will be much lower than those unexposed (as approximately 10% will be classified as small for gestational age), this sample size requirement was converted to reflect groups of unequal size with a ratio of 4:1 unexposed: exposed. This revised calculation suggests a required sample size of 155 in the exposed group and 618 in the unexposed group.

Figures presented in Table 4.1 represent the minimum sample size necessary in order to detect an effect of the specified magnitude. Ideally, other factors such as loss to follow up, the ability to adjust for potential confounding, and the need to detect potential effect modification should be taken into account in calculating required sample size. For the analysis used to calculate sample size in the present work – time to first live birth – by definition, all of the women included in the analysis experienced the outcome event. Therefore loss to follow up was nil and this factor was not taken into account in sample size considerations. There is a paucity of clear advice on how the inclusion of additional

covariates in an analysis affects sample size. In the context of case-control studies, Smith and Day suggest that an increase of 10% in sample size per confounding variable should be sufficient to ensure adequate power. They also note that only strong confounders (i.e. those strongly related to both the exposure and outcome) appear to have an effect on study power.[339] In terms of detecting possible effect modification, Smith and Day suggest that the sample size should be at least four times larger.[339]

To account for potential confounding, an overall increase in the sample size of 50% should be sufficient. This is equivalent to a sample size of 232 pregnancies in the exposed group and 925 pregnancies in the unexposed group. In order to have adequate power to detect potential effect modification, this number would need to be increased to 927 for the exposed group and 3705 for the exposed group. Taking into consideration the number of pregnancies potentially eligible for inclusion in the analyses, meeting these requirements seems unlikely and it may be that the analyses reported here are not sufficiently powered to detect effect modification.

4.2.4 Ethics

Ethical approval for UBCoS was gained from the Regional Ethics Committee at Karolinska Institute (dnr 03-117 and dnr 04-944, 10/03/03 and 10/12/04), and retrospectively from the London School of Hygiene's Research Ethics Committee [reference 5001, approval awarded 03/07/06].

4.3 DATA PREPARATION

4.3.1 Data coding, checking and cleaning

The data had already been subjected to significant checking and cleaning at source, but additional checks were made for inconsistencies in the data. This included range checks and looked in particular at exposure data. For example, implausible values for gestation were considered to be a gestational age of ≥48 weeks (births <30 weeks were excluded regardless). For birthweight, the lower plausible limit was considered to be <1000g and liveborn or <1500g and survived to childhood, with a maximum plausible value of 6000g. For categorical variables requiring codes to be assigned to different groups,

codes had already been assigned and the details of these codes were made available by the study coordinator.

4.3.2 Data manipulation

In utero growth

Four measures of *in utero* growth were taken from the dataset: birthweight, gestation, birthweight for gestational age, and ponderal index. In the original obstetric dataset, birthweight was measured to the nearest 10g. In the analyses reported here, birthweight was used as a binary variable, with <2500g classified as low birthweight and >2500g as normal birthweight. Gestation was calculated as the interval between the mother's reported last menstrual period and the date of delivery, dichotomised as <37 weeks (preterm) or >37 weeks (term). For birthweight for gestational age, sex-specific birthweight was standardised on a week by week basis (completed weeks), resulting in the creation of a within-cohort reference. Births were categorised as small for gestational age if the birthweight fell below the 10^{th} centile for completed gestational weeks. Birth length was recorded to the nearest 0.5cm, and was used to calculate ponderal index as a measure of weight relative to length (kg/m3). Ponderal index values were divided into quintiles, with the lowest quintile ('low ponderal index') compared to the remaining four fifths.

Other covariates

Other covariates were chosen from the dataset on the basis of their contribution to describing the sample and/or their role as potential confounders or effect modifiers of the association between markers of *in utero* growth and later fertility. Those covariates included in either one or both the analyses are listed in Table 4.2. The specific variables used in each analysis are described later in this chapter.

Civil status of G1 women was taken from the 1960 census, the first census linked to the UBCoS data and the only census to contain information on the year of the last change in civil status. Women were classified as unmarried, married, separated/divorced or widowed according to census categories. For women who reported their status as married, year of last change in civil status was taken as equivalent to the year of

marriage, and age at marriage was calculated using date of birth and the estimated date of marriage.

The age at marriage for husbands of G1 women was estimated using the date of birth of the father of the woman's first child, or where this was not available, the year of birth of her spouse as reported in the 1960 census. Where only the year of birth was available, the calendar day and month was estimated as the mid-year point (30th June).

Place of residence at the time of birth was taken from obstetric data and referred to whether women lived within the city of Uppsala or outside, in surrounding towns and villages (coded as 'other').

Continuous variables included the age of the woman's mother (G0) at the woman's birth (G1 birth), the age of both the G1 woman and her husband at marriage (if married), and the age of the G1 women at first birth (if parous). These data were categorised into five-year or ten-year groupings to ensure a reasonable spread of data.

Birth year was grouped in five year intervals (1915-1919, 1920-24, 1925-29) to mirror earlier analyses of UBCoS data which have grouped birth year in this way.[330, 332]

Socioeconomic status at birth was based on the father's occupation, and the fourteen original categories used in the obstetric records were reduced to six categories according to the Erikson-Goldthorpe class schema – higher non-manual, medium or lower non-manual, farmers or self-employed, higher manual, lower manual and other.[340]

Adult socioeconomic indicators were adapted from 1960 census categories. The twelve socioeconomic group categories used in the 1960 census were reduced to four: non-manual, manual, self-employed or farmer, and other or unknown. Education status was coded simply as elementary school or higher, although the census did subdivide this latter category, the numbers were considered to be too small for this analysis. The occupation of the woman at the time of the 1960 census was also extracted from the dataset, using a simple categorisation of 'in paid work', 'not in paid work', and 'not clear' (the latter category was coded as 'missing').

4.3.3 Choice of baseline groups

The choice of baseline group varied according to the variable under study. In most cases, there was an obvious baseline group, e.g. for the four main exposures, the baseline group was the default 'unexposed' category. For age categories, the second youngest category was chosen as the baseline rather than youngest category; this decision was taken to reflect biological norms and the undesirability of extremes in age for childbearing. For indicators of socioeconomic status, the baseline group was chosen as either the manual or lower manual group. For education level and occupational status in adulthood the largest group was taken as the baseline.

4.3.4 Inclusion criteria

The analyses were restricted to singleton born G1 women due to the relationship between multiplicity and size at birth. Women reported to be born before 30 weeks were also excluded, largely due to questionable data quality. The vast majority of women reported to be born below 30 weeks did not survive infancy; those that did are likely to have had gestation recorded incorrectly as survival at this gestation would have been unlikely among infants born at this time.

Only those women who had been linked to the multigenerational register and also to the 1960 census were eligible for inclusion in the analyses reported here. Linkage to the multigeneration register was required in order to ascertain the number (if any) of biological children born to each woman. The ability to trace women to the 1960 census ensured the collection of data on potential confounders and marital status (the latter necessary to calculate time to first birth).

4.4 ANALYSIS PLAN

All statistical analyses were carried out using Stata 9 and 10 (Stata Corporation, College Station, TX USA) and statistical significance was defined as $p<0.05$ for all analyses. All tests were two-sided unless otherwise specified.

4.4.1 Effect of early life factors on fertility rates

For this analysis, general and age-specific fertility rates were calculated using the number of live infants born to each G1 women during their 'fertile' years. These fertility rates were stratified according to a number of markers of *in utero* growth.

Sample

The inclusion criteria listed in 4.3.4 were initially applied to the sample. All women were subject to some period of observation during their reproductive years as the sample was limited to those still alive and resident in Sweden in 1960, by which point the women would have been aged 30-45. Missing outcome data was therefore minimal and limited to early censoring resulting from death or emigration before the end of the reproductive lifetime. Women with missing data on exposure status (birthweight, gestation/SGA status and ponderal index) were excluded for the relevant analyses. The resulting sample was used for all descriptive analyses, although missing information on covariates resulted in some further exclusions where comparisons necessitated the use of equivalent samples.

Fertility rates

Both general and age-specific fertility rates were calculated for the G1 sample. The general fertility rate (GFR) was calculated as the total number liveborn children born to a population of women aged 15-45 within one year, multiplied by 1000. Age-specific fertility rates were defined as the number of live births to a population of women within specific age bands between 15-45 in one year, multiplied by 1000. Details of children born were taken from the multigenerational register, and rates were calculated per infant born rather than per maternity. Rates were calculated according to the specific person time contributed by each woman during her reproductive years (15-45), with the events reported for each age band equivalent to the number of live births occurring to the total women in the age band. The denominator for each age group relates to the specific person time each woman contributed, with the majority of women contributing person time to all age bands, although those emigrating or dying before age 45 were lost to follow-up and censored accordingly.

Potential confounders and effect modifiers

Period of birth (birth cohort) classified into five-yearly groupings was included as an *a priori* confounder in all analyses in line with earlier analyses of UBCoS data.[330] Other confounders considered in the analyses included demographic and socioeconomic characteristics at birth and adulthood.

Maternal age (G0) at the time of the G1 woman's birth was considered a potential confounder, with maternal age associated with adverse perinatal outcomes and early life factors[108, 341-344] and some inconsistent evidence that there may also be an association between age at motherhood and the fertility of the ensuing daughter.[23, 55] It was hypothesised that socioeconomic group and other markers of socioeconomic position at birth (place of residence and maternal civil status) may be associated with early life factors, although any effect on later fertility was thought to be less plausible.

Three adult socioeconomic indicators were also chosen as potential confounders. It seemed possible that household socioeconomic class, education level and occupation of the woman may all be independently associated with fertility and early life factors.

Statistical analysis

To begin, visual displays of the distribution of the four exposure variables (early life factors, in this case four markers of *in utero* growth) were presented. For univariate analysis the characteristics of the main UBCoS sample (sample 1) were described according to number of women contributing time to the analysis and the number of women experiencing at least one birth. The crude fertility rate was presented for each exposure and covariate. General fertility rates were calculated using Poisson regression and stratified by exposure level. A Lexis expansion was performed to enable the calculation of age-specific fertility rates. Age-specific rates and crude fertility rate ratios were presented for each exposure level. The effect of potential confounders was explored through multivariate Poisson regression adjusting for the effect of ageband and other potential confounders. In multivariate analysis, standard errors were calculated using the robust method to take into account clustering by woman (some women having more than one birth). A forward stepwise strategy was used, entering each potential confounder one by one in order of strength of association with the outcome (fertility

rate). Association between covariates and exposure factors was explored, and those variables identified as independently associated with both exposure and outcome were entered in the model first. Confounding was considered likely if a factor changed the estimation of the fertility rate ratio (FRR) by 10% or more, or changed the FRR from significant (using the threshold $p < 0.05$) to non-significant or vice-versa. All covariates not retained as part of the model-building process were checked one last time with the final model. Where appropriate, ordinal variables were tested for linearity and were entered in the model as linear terms if the fit was acceptable. Specified *a priori* effect modifiers were tested using an interaction term and assessed using a likelihood ratio test. If no covariates were shown to be definite confounders, the decision was taken to adjust for birth cohort and socioeconomic position at birth (consistent with previously published studies) rather than presenting unadjusted rate ratios. The results of final models were presented as fertility rate ratios, equivalent to Poisson rate ratios.

4.4.2 The effect of early life factors on time to first live birth

The second analysis used time to first live birth (TTFLB) as the main outcome. TTFLB was calculated as the interval between estimated date of marriage (as a proxy for first exposure to pregnancy) and the birth of the first liveborn child among those women experiencing at least one live birth. Census data only captured the year of marriage, so the actual date of marriage had to be estimated. The data were explored using three different estimates of the marriage date: 1st January (year beginning), 30th June (mid-year point), and 31st December (year end). The mid-year point (30th June) was chosen for use in the main analyses. A series of sensitivity analyses comparing different estimations of the marriage date along with an analysis based on time to first live birth as a binary variable (using year of marriage only rather than an estimation of the exact date) were carried out to check for similarity of results. Further details of these analyses are provided below.

Sample

Taking the sample described previously (for the analysis looking at the effect of early life factors on fertility rates) as a starting point, further exclusions were applied to this sample to produce the sample used this analysis. This sample was restricted to women who married and those for whom the year of marriage was available. Information on

marital status was collected during each available census (1960, 1970 and 1980), however, timing of marriage was only collected in the 1960 census. The information collected was termed "last change in civil status", which in practice referred to the year of marriage for those whose civil status was defined as 'married'. The sample was therefore limited to those whose civil status was defined as married in the 1960 census, regardless of any later changes in marital status. The sample was further restricted to those who married during their reproductive years (<40 years) and whom began their childbearing after marriage (those who had no births recorded before marriage). This process resulted in a sample of married women with at least one live birth, who had married during their reproductive years and had no pre-marital births. Again, a small number of women were excluded from the relevant analyses due to missing data on exposure status (markers of *in utero* growth). Data on covariates was mostly complete, but comparisons between adjusted models necessitated a few further exclusions in order to guarantee comparability between models.

Potential confounders and effect modifiers

As before, birth cohort was considered an important *a priori* confounder for all analyses. Similarly, the age of the G1 woman's mother at her birth, maternal civil status, place of residence at birth and socioeconomic class at birth were also investigated as potential confounders.

Because of considerable evidence supporting an association between age and fertility,[99] age at marriage was chosen as a possible confounder of the relationship between markers of *in utero* growth and time to first birth. The effect of increasing age on male fertility is less clear,[114] but some suggestion of an association confirmed the decision to include male age at marriage as a potential confounder of the association between *in utero* growth and time to first birth. In addition, socioeconomic indicators such as household socioeconomic class, level of education and occupation were also considered potential confounders.

Statistical analysis

For univariate analysis, the data were first explored using the more restricted sample (sample 2) according to various characteristics and the median time to first live birth.

Crude fecundability ratios (FR, equivalent to hazard ratios) were presented for the association between each exposure and time to first birth. Kaplan Meier graphs were used to provide a visual display of the time to first live birth according the main exposure variables and other variables of interest. Log-rank tests were performed on these Kaplan Meier graphs.

A series of Cox's proportional hazards models were used to investigate the effect of each exposure factor on time to first live birth. The analysis was modelled using time under observation as the time scale, with women entering the model at date of marriage and exiting at the time of event (birth of first liveborn child). Multivariate Cox models were constructed using a forward stepwise strategy, with a separate model built for each of the four exposures. All covariates were only retained in the model if they changed the FR by at least 10% or changed the significance of the FR. Covariates were entered into the model in order of strength of association with the outcome (time to first live birth). Once the final model was decided, each excluded covariate was checked one last time for confirmation. Where appropriate, ordinal variables were tested for linearity and were entered in the model as linear terms if the fit was acceptable. Specified *a priori* effect modifiers were tested using an interaction term and assessed using a LRT. If no potential confounders appeared to produce a confounding effect, it was decided to include certain variables in the model for comparative purposes. As with the sample described previously, birth cohort and socioeconomic position at birth were chosen for definite inclusion. In line with conventional time to event analysis methods, a fecundability ratio of <1.00 indicated that the exposed group experienced a slower time to outcome (a longer overall TTFLB), with the reverse true for a fecundability ratio of >1.00.

Two sensitivity analyses were carried out to confirm the final results. The first sensitivity analysis compared the crude hazard ratios (calculated using Cox regression as before) for the association between each exposure factor on time to first live birth using different estimations of the marriage date (1st January, year beginning; 30th June, mid-year point; 31st December, year end). A second sensitivity analysis looked at the association between each main exposure factor and time to first birth categorised as a binary variable (first live birth the year after the year of marriage vs. first live birth two

or more years after the year of marriage). This latter analysis used only the year of marriage and thus avoided potential bias resulting from the estimation of exact date of marriage. Logistic regression was used to calculate crude odds ratios for this analysis. In contrast to fecundability ratios calculated using Cox regression, an odds ratio of <1.00 indicated a protective effect of the exposure, i.e. that compared to the unexposed group, the exposed group had a higher odds of giving birth within two years of marriage.

Table 4.1: Estimated sample size for Cox regression

Power	Alpha[1]	Hazard ratio	N[2]
0.80	0.05	0.10	6
0.80	0.05	0.20	13
0.80	0.05	0.30	22
0.80	0.05	0.40	38
0.80	0.05	0.50	66
0.80	0.05	0.60	121
0.80	0.05	0.70	247
0.80	0.05	0.80	631
0.80	0.05	0.90	2829

[1]Two-sided test
[2]Number of events (pregnancies) required in each group (exposed and unexposed)

Table 4.2: Variables used in the analyses

Birth characteristics	Adult characteristics
Birthweight*	Age at marriage
Gestation*	Husband's age at marriage
Birthweight for gestational age*	Socioeconomic class (household)
Ponderal index*	Level of education
Year of birth	Occupation
Mother's age at birth	*Age at first birth*
Mother's civil status	*Parity*
Residence	
Socioeconomic class	

*early life factors (exposures)

Chapter 5: Uppsala Birth Cohort Study Multigen – Results

This chapter presents the results of the analyses described in Chapter 4, specifically:

- To describe the characteristics of this sample of women
- To present and interpret general and age-specific fertility rates according to specific early life factors relating to *in utero* growth (preterm birth, low birthweight, small for gestational age status, and low ponderal index)
- To determine the effect of the above mentioned early life factors on estimated time to first birth among a sample of married women in the UBCoS cohort.

5.1 CHARACTERISTICS OF POPULATION

The main sample for these analyses consisted of all UBCoS G1 women who survived to adulthood and were traced in the 1960 census, all of whom had at least a period of their reproductive years observed. From the original 6977 female infants traced as part of the original UBCoS cohort, 5505 women were included in this sample (Table 5.1). The process by which this sample was reached is described in Figure 5.1 and shows the original G1 women who were retained in the final sample by year of birth. A more restricted sample was used for the investigation of the effect of early life factors on time to first live birth. The process by which this specific sample was reached is described later in this chapter.

5.1.1 Markers of early life growth

As a preliminary step before any formal analysis, the main sample was examined in terms of the proxy measures of *in utero* growth which formed the focus of these analyses.

Birthweight

Birthweight was available for 5499 of the 5505 women included in the sample, with values presented in Figure 5.2. Values ranged from 1510-5400 grams, with a mean birthweight of 3397 grams (sd 497) and median 3400 grams. Two hundred and

seventeen women had a birthweight of less than 2500 grams. Overall, birthweight values were very slightly left skewed (skewness statistic -0.088).

Gestation

Information on gestational age was missing for 158 women. Gestational age ranged from 30 to 47 weeks, with a mean of 39.5 weeks (sd 2.06) and median of 40 weeks. Gestational age values were skewed to the left (skewness statistic -0.599), this is clearly visible in the histogram displayed as Figure 5.3.

Small for gestational age status

Small for gestational status was calculated for 5341 women for whom birthweight and gestation was available. Figure 5.4 shows the values of birthweight plotted again gestational age for these women. Transposed on this graph is the mean birthweight for each completed gestational week plotted in blue, and the birthweight value for the 10^{th} centile at each completed gestational week plotted in red. Values falling below the 10^{th} centile were taken as representing 'small for gestational age'. The positive association between birthweight and gestational age is clearly visible on this plot, though slight dips at lower gestational ages (around 32-33 weeks) and higher gestational ages (45 weeks) can be observed. These are almost certainly attributable to the smaller number of births occurring at these gestations, resulting in less robust estimates of optimal birthweight.

Ponderal index

Ponderal index was available for 5484 women, with an range of 13.3 – 52.9 (mean 26.4, sd 2.7). Table 5.2 presents ponderal index quintiles by the mean, standard deviation and range of the ponderal index values compromising each quintile. Birthweight values and length are also presented for each ponderal index quintile. The lowest and highest ponderal index quintiles cover a wider range of ponderal index values than the intervening quintiles.

5.2 EFFECT OF EARLY LIFE FACTORS ON FERTILITY RATES

5.2.1 Selection of sample

All 5505 women who were traced in the 1960 census were eligible to contribute person-time to the analysis focussing on fertility rates. Of these 5505 women, six women had missing information on birthweight, 158 women had missing information on gestation, 164 had missing information on SGA status, and 21 women had missing information on ponderal index. These women were excluded for the relevant analyses. There were a small number of missing values for some covariates, although no analysis was affected by more than four percent missing data. Women with missing data on one covariate or more were included in descriptive analyses. To ensure internal validity, a small number of women with data missing on covariates were excluded where comparisons between different adjusted rates were performed. The number of women potentially excluded for this purpose is detailed in Figure 5.5.

5.2.2 Characteristics of sample

Overall, women contained in this analysis experienced a total of 10471 births over 164,894 person-years. This is equivalent to an overall fertility rate of 63.5 births per 1000 person-years (95% CI 62.3, 64.7).

Early life factors: markers of in utero growth

The number of women contributing person-time and the crude fertility rates for each strata of main exposure factor are presented in Table 5.3. Overall, four, seven, eight and 16% of women contributing time to this analysis were respectively classified as low birthweight, preterm, small for gestational age and low ponderal index. The crude fertility rates for women stratified by these early life factors are similar, with all rates between 59-64 live births per 1000 person-years. The fertility rate for women born low birthweight, preterm, small for gestational age and of low ponderal index are all very slightly lower than the corresponding baseline categories, but with overlapping 95% confidence intervals and non-significant crude fertility rate ratios.

Sociodemographic characteristics at birth

Table 5.4 presents the distribution of sociodemographic characteristics at birth according to the number of women contributing to the analysis and the crude fertility rates stratified by these variables.

Year of birth was grouped into five yearly periods, with a quarter of women born in the first period (1915-1919), and 34% and 40% respectively born in the latter two periods (1920-24, 1925-29). There appears to be a significant trend for women born in successive birth cohorts to experience a higher fertility rate (58, 63 and 68 births per 100 person-years for births in 1915-19, 1920-24 and 1925-29 respectively).

Eighty-six percent of women were born to mothers aged between 20-39 at birth, with similar proportions above and below this age range. There is a slight suggestion of a U-shaped trend with regard to fertility, whereby those with the youngest and those with the oldest mothers have a higher general fertility rate. However, this trend was not statistically significant.

Twenty percent of women were born to a mother whose civil status was reported as 'single' at the time of their birth, one percent born to women who were divorced or widowed, and the remainder born to married women. Those women born to single mothers were associated with a significantly slightly increased fertility rate compared to those whose mothers were married (67 vs. 62 per 1000 person-years).

Approximately half the women contributing to the analysis had their family home in Uppsala city, with the remaining half living in surrounding towns and villages. Women whose family residence was outside Uppsala city at the time of their birth were associated with a slightly higher fertility rate.

Overall, about one quarter of women were born into families with non-manual socioeconomic status, 51% to families with a manual background, and the remainder born into families where the head of household was either a farmer, self-employed, or had another non-classified occupation. There were no clear-cut trends with regard to socioeconomic class at birth, with fertility rates similar across all groups.

Sociodemographic characteristics in adulthood

Five sociodemographic factors in adulthood were investigated in univariate analysis: age at marriage, age at first birth, socioeconomic class at 1960 census, occupation at 1960 census, and education level (Table 5.5).

The vast majority of women (77%) married during their twenties. Eleven percent married under the age of 20, and 12% at age 30 or older. Nearly nine hundred women were not recorded as 'married' during the 1960 census. Although a small number of these women were likely to have stayed unmarried throughout their adult years, other women may have had changes in civil status recorded in later censuses (age at marriage was not available for these women though, due to changes in census data collection). In those women for whom age at marriage data were available, a younger age at marriage was associated with a markedly higher fertility rate. There was a clear trend for fertility rates to decline with increasing age at marriage. However, only the fertility rate for the youngest age category differed more markedly (96 per 1000 person-years vs. 49-73 births per 1000 person-years for other age categories), with confidence intervals not overlapping with the other age-specific rates.

Among those women who had at least one child, nearly three-quarters had their first child between 20-29. Twelve percent had their first birth below age 20, and 14% at age 30 or over. Seventeen percent of women did not experience a livebirth during the time observed. As expected, age at first birth was significantly associated with fertility rates.

Of the adult socioeconomic indicators, just over half the women were classified as being in a non-manual socioeconomic class at the time of the 1960 census, with 35% from a manual household and the remainder classified as from a self-employed class. The vast majority of women (95%) had only an elementary school education, and nearly two-thirds of women (63%) were not in paid work themselves. Only household socioeconomic class and the woman's own occupation in 1960 were significantly associated with crude fertility rate. In terms of household socioeconomic class, women from non-manual households had a lower fertility rate compared to the baseline manual

group. Women in paid work had a lower fertility rate compared to those who did not work.

5.2.3 Age-specific fertility rates

In order to take into account changing fertility rates with age, a Lexis expansion was performed and age-specific fertility rates were calculated. These age-specific fertility rates represent the fertility experience of the cohort during the specific age range indicated by the age bands. These age specific rates are presented stratified by the main exposures (factors related to *in utero* growth) in Table 5.6, Table 5.7, Table 5.8 and Table 5.9. We can see from these tables that fertility rates vary widely according to age group and regardless of exposure status, peaking in the age 25-<30 age group and lowest in those aged 40-<45. For women born low birthweight and women born preterm, the majority of their age-specific fertility rates are slightly lower than for women categorised with normal birthweight and term gestation. With both birthweight for gestational age and low ponderal index compared to the comparison group, fertility rates vary in a less clear-cut pattern. Neither of these two exposure factors appear to be consistently associated with fertility rates in this population. The crude fertility rate ratios presented in these tables provide no suggestion of an association between early life factors and fertility rates.

5.2.4 Fertility rate ratios stratified by covariates

Table A.1.1 presented in Appendix 1 displays rate ratios summarising the effect of early life factors on fertility rates stratified by risk factors considered significant in univariate analysis and *a priori* confounders.

5.2.5 Fertility rate ratios adjusted for potential confounding

As described in the previous chapter, the effect of potential confounding factors on the association between early life factors and fertility rates was explored. Variables that were significantly associated with fertility rates in univariate analysis (Table 5.4 and Table 5.5) were taken forward and considered as possible confounding factors. The exception to this was age at first birth, which although associated with fertility (those marrying at younger ages associated with higher fertility rates), was only available for the sub-sample of women who were married at the time of the 1960 census. The

remaining factors (birth cohort, mother's civil status, place of residence, and socioeconomic group at birth) were entered into Poisson models considering each of the markers of *in utero* growth as the main exposure factor. Ageband was also included in each of these models. The fertility rate ratios resulting from each of these models is reported in Table A.1.2 (Appendix 1). In summary, there was no evidence that any of these factors confounded the association between markers of *in utero* growth and general or age-specific fertility rates. However, a decision was made to retain birth cohort and socioeconomic group at birth as *a priori* confounders in preference to presenting unadjusted rate ratios.

5.2.6 Final fertility rate ratios for the association between markers of in utero growth and fertility rates

Final fertility rate ratios adjusted for age, birth cohort and socioeconomic group at birth are presented alongside age-specific rate ratios in Table 5.6, Table 5.7, Table 5.8 and Table 5.9. The adjusted fertility rate ratios calculated for fertility rates stratified by low birthweight status are presented in Table 5.6. These results confirm that although fertility rates vary considerably by age, this trend is similar for all women regardless of birthweight status. Therefore, these results provide no evidence low birthweight is associated with fertility rates in these women. Preterm birth is the focus of Table 5.7. Again, there is no evidence from these results to suggest that fertility rates differ according to whether a woman was born at a preterm gestation. The adjusted fertility rate ratios presented in Table 5.8 report adjusted ratios for the association between small for gestational age and age-specific fertility rates in adulthood. Despite slight fluctuations in the fertility rate ratios, again there is no evidence to support the hypothesised association between restricted growth *in utero* and later fertility. Finally, Table 5.9 reports the results for low ponderal index. The fertility rate ratios presented in this analysis are all close to 1 and provide no evidence for an association between low ponderal index and fertility rates.

5.3 EFFECT OF EARLY LIFE FACTORS ON TIME TO FIRST LIVE BIRTH

5.3.1 Sample

The process by which the sample for this analysis was reached is detailed in Figure 5.6. Of the 5505 women who comprise Sample 1, 4646 women were classified as married according to the 1960 census. Twenty-five of these women married at aged 40 or over, and were excluded from the sample. A further 879 women were excluded as they had at least one live birth before marriage. This final sample for this analysis consisted of 3264 women whom had at least one live birth subsequent to marriage, allowing for time to first live birth (TTFLB) to be calculated using the strategy discussed in 4.4.2. The exclusions reported here are also detailed by year of birth in Table 5.1. Five, 95 and 10 women were excluded due to missing data on birthweight, gestation/SGA status and ponderal index respectively (Figure 5.7). Only a small number of women had missing data on specific covariates, these women were included in descriptive analyses but excluded where comparisons necessitated the use of an equivalent sample.

5.3.2 Characteristics

Time to first live birth

Forty-two percent of women had a time to first live birth of 12 months or more, and 20% 24 months or more. A cumulative Kaplan-Meier curve for time to first live birth is displayed as Figure 5.8.

Early life factors: markers of in utero growth

The distribution of low birthweight, preterm birth, low birthweight for gestational age, and low ponderal index among the 3264 women meeting the inclusion criteria for this analysis was four, seven, eight and sixteen percent respectively (Table 5.10). The median time to first birth was very slighter shorter for women both low birthweight and those women born small for gestational age compared to the baseline categories (normal birthweight and appropriate weight for gestational age). The reverse was true for ponderal index and gestation, with those born preterm and those born with a lower ponderal index experiencing a longer median interval to first birth compared to the corresponding baseline categories. The crude fecundability ratios (which compare

overall TTFLB) suggest that women born low birthweight, preterm and of low ponderal index appear to experience a slightly longer TTFLB overall when compared to unexposed women. Conversely, women born small for gestational age appear to experience a slighter shorter TTFLB overall when compared to women born an appropriate weight for gestational age. However, none of the fecundability ratios summarising the relationship between early life factors and time to first live birth were statistically significant in the crude analysis.

Sociodemographic characteristics at birth

The distribution of sociodemographic factors at birth was similar for this restricted sample (Table 5.11) compared to the full sample used in the analysis of fertility rates. There was a trend whereby later birth was associated with a shorter time to first live birth, and this was supported by statistically significant fecundability ratios (equivalent to hazard ratios). No clear patterns were obvious for the relationship between both mother's age at birth and maternal civil status and time to first live birth. Residence outside Uppsala city was associated with a shorter time to first live birth. Using lower manual background as the reference category, both women whose socioeconomic class at birth was higher non-manual or farmers/self-employed had a slightly longer time to first live birth.

Sociodemographic characteristics in adulthood

Associations between sociodemographic factors in adulthood and time to first live birth are presented in Table 5.12. Both the age of marriage of the woman and her husband were investigated in univariate analysis. Although rates varied by age, only the youngest age categories (<20 for women, <25 for men) were significantly associated with a shorter time to first live birth when compared to the reference category (20-24 for women, 25-29 for men). In terms of adult socioeconomic class, both non-manual and self-employed socioeconomic classes had a higher time to first live birth compared to women from manual socioeconomic classes. Neither level of education or occupation (in paid work vs. no paid work) measured during the 1960 census were associated with time to first live birth.

5.3.3 Time to first live birth – survival curves

A series of figures are presented displaying the Kaplan Meier survival curves for time to first live birth according to a range of covariates (Figure 5.9, Figure 5.10, Figure 5.11, Figure 5.12, Figure 5.13, Figure 5.14, Figure 5.15, Figure 5.16, Figure 5.17).

Figure 5.9 shows the proportion of women conceiving their first live birth by months since the estimated date of their marriage, according to their birthweight category. The two event curves are similar overall (log rank test p 0.44), though there is a slight trend for women born low birthweight to conceive faster in the first eighteen months subsequent to marriage, though in later months this trend is reversed. Figure 5.10 presents the event curves by gestation category. Women start off with similar risk of conception regardless of gestation status, the curves then separate very slightly after twelve months and suggest that women born at term gestations conceive faster at this point onwards until around 48 months when the curves coincide again (log rank test p 0.30). Event curves by small for gestational age status are presented as Figure 5.11. Again, the two curves are very similar (log rank p 0.44), with no obvious difference in the likelihood of conception according to birthweight for gestational age status. Time to first live birth since marriage is compared in Figure 5.12 according to ponderal index at birth. Although the two curves are close together at the beginning and end of this plot, they separate slightly during (approximately) months 10-72 with women with the lowest quintile of ponderal index at birth taking on average slighter longer to conceive their first live birth (log rank test p 0.12).

Event curves were also plotted according to other important covariates. Birth cohort showed an association with time to first live birth, with those born earliest (1915-1919) being quickest to conceive, and those born most recently (1925-1929) taking the longest (Figure 5.13, log rank test p <0.001). The pattern with regard to socioeconomic status was less clear. Women born into higher non-manual and farmers or self-employed groups conceived quickest, with the other groups ('other', higher manual and medium/lower non-manual) showing a similar curve (Figure 5.14, log rank test p <0.01). Women born outside Uppsala also had a quicker time to first live birth (Figure 5.15, log rank test p <0.001). In terms of age at marriage (Figure 5.16), women married at less than 20 had a significantly faster time to first live birth, with rates for other age

groups mostly similar although 35+ curve was initially higher (log rank test, p <0.001). Lastly, Figure 5.17 shows time to first live birth according to adult socioeconomic group. This figures shows that women in manual socioeconomic groups at the time of the 1960 census conceived the quickest with the slowest rate observed among women in non-manual groups (log rank test p <0.001).

5.3.4 Fecundability ratios stratified by covariates

Crude fecundability ratios for the association between early life factors and time to live first birth stratified by covariates significant at the univariate stage and *a priori* confounders are presented in Table A.1.3. These results provide little evidence of a clear pattern of effect modification and as the analysis was not sufficiently powered to investigate effect modification, this was not explored in any further analyses.

5.3.5 Fecundability ratios adjusted for potential confounders

Six covariates showed some association with time to first live birth in univariate analysis: time period of birth, residence at birth, socioeconomic class at birth, age at marriage, husband's age at marriage, and socioeconomic class in adulthood. Fecundability ratios summarising the association between each marker of *in utero* growth and time to first live birth and adjusted for each of these covariates in turn were calculated. These results are presented in Table A.1.4 in Appendix 1. From these results we can see that there is little evidence of confounding. Although there are small variations in the fecundability ratios after individual adjustment by some of these covariates, the degree of variation is <10% and does not change the significance (or non-significance) of the results.

5.3.6 Final fecundability ratios for the association between early life factors and time to first live birth

The final adjusted fecundability ratios summarising the association between markers of *in utero* growth and time to first live birth are presented in Table 5.13. These ratios are adjusted for birth cohort, socioeconomic group at birth, and age at marriage. Adjustment for these variables resulted only in minimal differences in the reported rate ratios. These results provide little evidence that any of these proxy measures of *in utero* growth are associated with time to first live birth in this analysis of UBCoS Multigen data.

5.3.7 Sensitivity analyses for the association between early life factors and time to first live birth

Comparing estimation of marriage date

Crude fecundability ratios for the association between markers of *in utero* growth and time to first live birth according to different estimations of the marriage date are presented in Table 5.14. This comparison shows that the choice of estimated marriage date has little impact on results, with crude fecundability ratios and confidence intervals very similar or identical across the three choices of estimated marriage date (beginning, mid-year point, and year end).

Time to first live birth as a binary variable

A further sensitivity analysis for the association between markers of *in utero* growth and time to first live birth is presented in Table 5.15. In this analysis, time to first live birth was investigated as a binary variable, with the proportion of women who experienced their first live birth the year after the year of marriage compared to those who experienced their first live birth two years or more after the year of marriage. As with the main analysis, these results do not provide evidence of an association between markers of *in utero* growth and time to first live birth. The crude odds ratios suggest that women born low birthweight, those born preterm, and those with a lower ponderal index appear to be less likely to have their first child the year after marriage compared to women in the corresponding baseline categories. This is similar to the (non-significant) trend observed in the main analysis, whereby women from these groups appeared to be associated with a slightly longer TTFLB. However, the trend for women born small for gestational age is in the opposite direction, i.e. these women appear to be more likely to experience their first birth the year subsequent to marriage. Again, this is in line with the findings in the main analysis.

Figure 5.1: Flowchart of main study sample (sample 1)

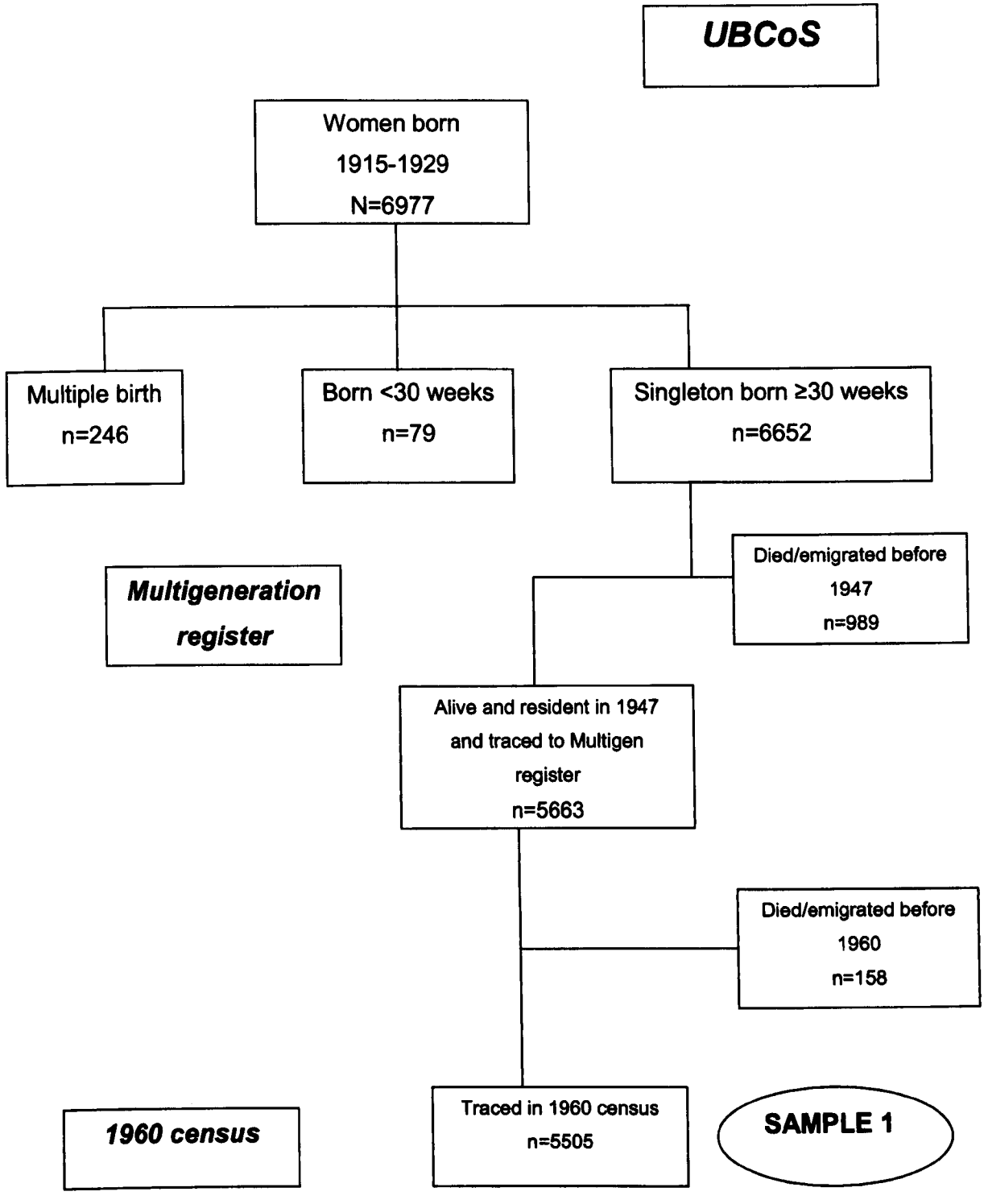


Table 5.1: Breakdown of study sample by year of birth (sample 1 and sample 2)

Year of birth	Born	Singleton	Born ≥30 weeks	Alive and resident in 1960	Traced in 1960 census	Civil status in 1960 census: "married"	Age at marriage <40	no birth before marriage	At least one live born child
1915	353	345	344	281	259	205	198	171	145
1916	401	383	381	335	313	253	245	206	171
1917	363	345	342	296	272	219	216	179	151
1918	369	360	353	302	282	237	233	197	162
1919	405	396	393	347	329	282	279	231	203
1920	469	459	453	387	359	298	298	248	209
1921	498	481	475	407	383	315	315	261	232
1922	436	420	409	352	330	285	285	230	206
1923	479	455	454	398	383	333	333	280	240
1924	496	479	473	414	396	343	343	260	222
1925	519	504	502	453	431	359	359	292	255
1926	537	513	507	432	415	360	360	282	254
1927	546	526	522	465	441	390	390	307	273
1928	561	542	530	485	469	397	397	314	275
1929	545	523	514	468	443	370	370	284	266
TOTAL	**6977**	**6731**	**6652**	**5822**	**5505**	**4646**	**4621**	**3742**	**3264**

SAMPLE 1

SAMPLE 2

Figure 5.2: Distribution of birthweight values across main sample (n=5499)

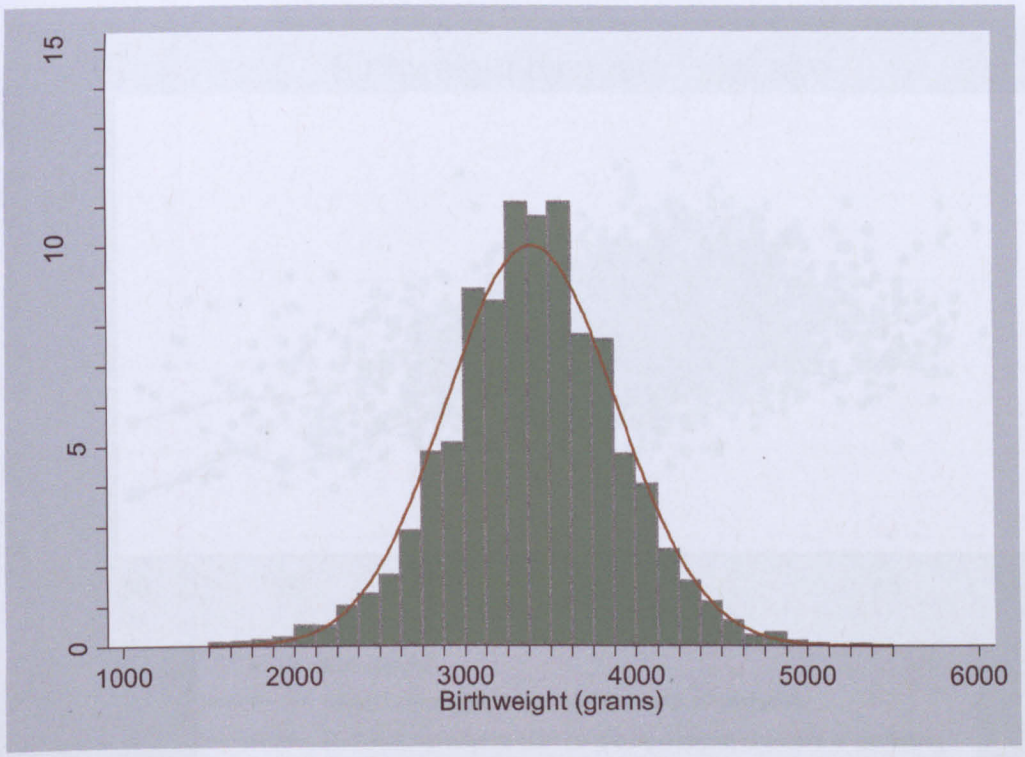


Figure 5.3: Gestational age across main sample (n=5347)

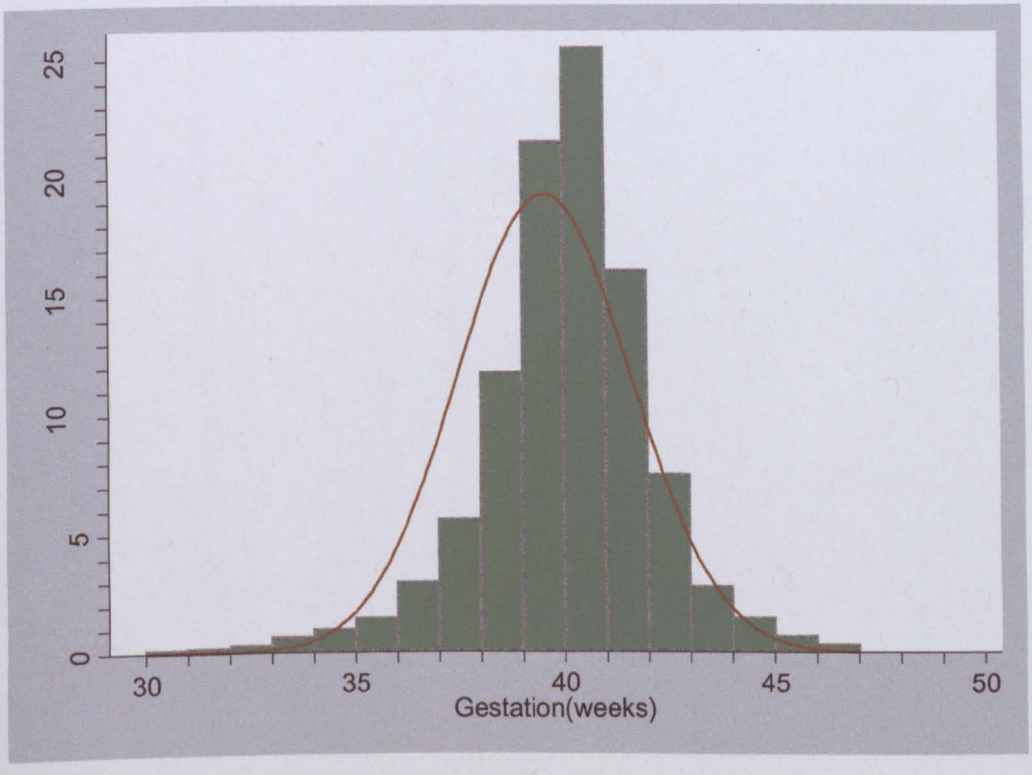


Figure 5.4: Birthweight by gestational age across main sample (n=5341)

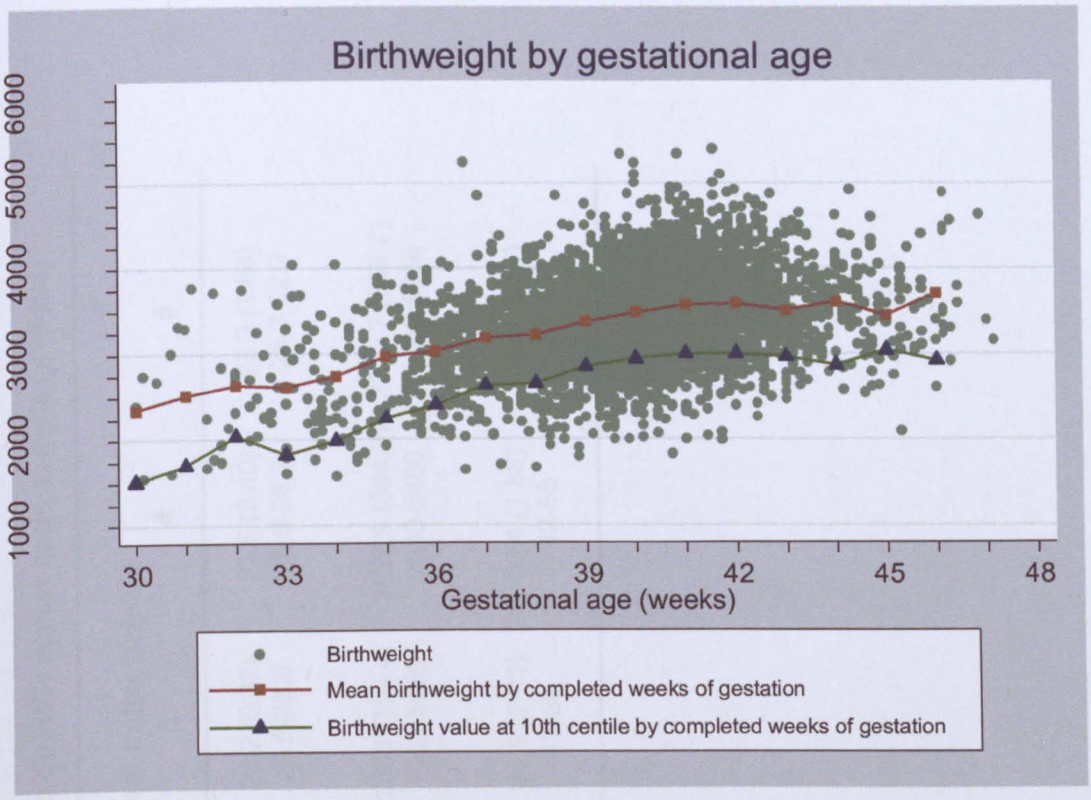


Table 5.2: Ponderal index values, birthweight and length by ponderal index quintile across main sample (n=5484)

		Ponderal index quintile				
		1	2	3	4	5
Ponderal index (kg/m^3)	Mean (SD)	22.5 (1.40)	24.8 (0.46)	26.2 (0.37)	27.5 (0.40)	29.9 (1.88)
	Range	13.3-23.9	24-25.5	25.6-26.8	26.9-28.2	28.3-52.9
Birthweight (g)	Mean (SD)	3007 (489.4)	3225 (419.4)	3383 (399.4)	3529.9 (394.0)	3310.7 (658.7)
	Range	1510-4580	1700-4800	1900-5000	2030-5400	1700-5350
Length (cm)	Mean (SD)	51.0 (2.84)	50.6 (2.22)	50.5 (2.01)	50.4 (1.88)	50.0 (2.14)
	Range	40-59	41-58	42-58	42-58	34-55

Figure 5.5: Exclusions for sample 1 (fertility rates)

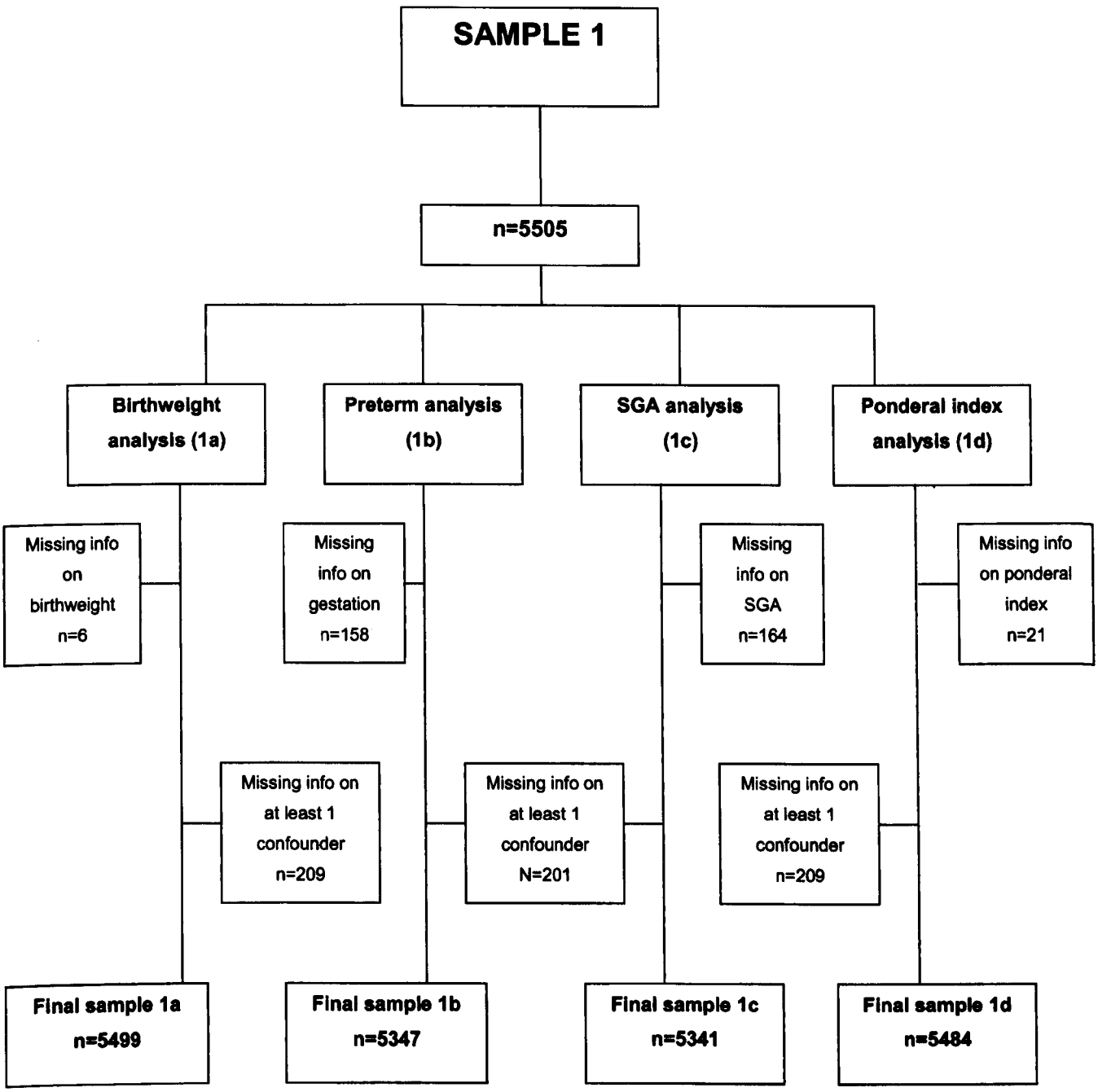


Table 5.3: Fertility rates and fertility rate ratios according to early life factors

		No. of women contributing person-time		No. of live births	Fertile person-time	Fertility Rate	Crude Fertility Rate Ratio
		n	(%)	n	(1000 py)	(95% CI)	(95% CI)
Early life factors							
Birthweight	<2500g	217	(3.9)	385	6.5	59.2 (53.6, 65.5)	0.93 (0.84, 1.03)
	≥2500g	5282	(96.1)	10071	158.2	63.6 (62.4, 64.9)	1
	Missing	6					
Gestation	<37 weeks	361	(6.8)	659	10.8	60.9 (56.4, 65.7)	0.96 (0.88, 1.04)
	≥37 weeks	4986	(93.2)	9502	149.3	63.6 (62.4, 64.9)	1
	Missing	158					
Birthweight for gestational age	<10th centile	441	(8.3)	832	13.2	63.0 (58.9, 67.4)	0.99 (0.92, 1.07)
	≥10th centile	4900	(91.7)	9314	146.8	63.5 (62.2, 64.8)	1
	Missing	164					
Ponderal index	Lowest quintile	902	(16.4)	1671	27.0	61.8 (58.9, 64.8)	0.97 (0.92, 1.02)
	2-5th quintile	4582	(83.6)	8756	137.2	63.8 (62.5, 65.2)	1
	Missing	21					

Table 5.4: Fertility rates and fertility rate ratios according to sociodemographic characteristics at birth

		No. of women contributing person-time		No. of live births	Fertile person-time	Fertility Rate	Crude Fertility Rate Ratio
		n	(%)	n	(1000 py)	(95% CI)	(95% CI)
Birth characteristics							
Year of birth	1915-1919	1455	(26.4)	2529	43.6	57.9 (55.7, 60.2)	1
	1920-1924	1851	(33.6)	3480	55.5	62.7 (60.7, 64.9)	1.08 (1.03, 1.14)**
	1925-1929	2199	(33.9)	4462	65.8	67.8 (65.9, 69.8)	1.17 (1.11, 1.23)***
Age of woman's mother at her birth	<20	302	(6.7)	587	9.06	65.9 (60.8, 71.4)	1.03 (0.96, 1.17)
	20-29	2015	(44.8)	5759	90.3	63.8 (62.1, 65.4)	1
	30-39	1843	(40.9)	3416	55.2	61.9 (59.9, 64.0)	0.97 (0.93, 1.01)
	≥40	341	(7.6)	683	10.2	66.8 (62.0, 72.1)	1.05 (0.97, 1.14)
	Missing	4					
Civil status of woman's mother at her birth	Married	4363	(79.4)	8169	130.7	62.5 (61.2, 63.9)	1
	Single	1085	(19.8)	2176	32.5	67.0 (64.2, 69.8)	1.07 (1.02, 1.12)**
	Divorced/widowed	44	(0.8)	97	1.3	73.5 (60.2, 89.7)	1.18 (0.96, 1.44)
	Missing	13					
Residence	Uppsala	2610	(47.5)	4961	78.2	60.6 (58.3, 61.7)	1
	Other	2888	(52.5)	5772	86.5	66.7 (65.0, 68.5)	1.11 (1.07, 1.16)***
	Missing	7					
Socioeconomic class at birth	higher non-manual	418	(7.6)	799	12.5	63.9 (59.6, 68.5)	1.02 (0.94, 1.10)
	medium/lower non-manual	927	(16.8)	1736	27.8	62.5 (59.6, 65.5)	0.99 (0.94, 1.05)
	farmers or self-employed	921	(16.7)	1807	27.6	65.5 (62.6, 68.6)	1.04 (0.98, 1.10)
	higher manual	807	(14.7)	1502	24.2	62.1 (59.0, 65.3)	0.99 (0.93, 1.05)
	lower manual	1980	(36.0)	3733	59.3	62.9 (60.9, 65.0)	1
	other	452	(8.2)	894	13.5	66.0 (61.8, 70.5)	1.05 (0.98, 1.13)

***p <0.001 **p <0.01 ***p<0.05

Table 5.5: Fertility rates and fertility rate ratios according to adult sociodemographic characteristics

		No. of women contributing person-time n	(%)	No. of live births n	Fertile person-time (1000 py)	Fertility Rate (95% CI)	Crude Fertility Rate Ratio (95% CI)
Adult characteristics							
Age at marriage (if married)	<20	504	(10.8)	1449	15.1	95.9 (91.1, 100.9)	1.30 (1.23, 1.39)***
	20-24	2320	(49.9)	5112	69.5	73.5 (71.5, 75.6)	1
	25-29	1269	(27.3)	2352	38.0	61.9 (59.4, 64.4)	0.84 (0.81, 0.88)***
	30-34	420	(9.0)	645	12.6	51.3 (47.5, 55.4)	0.70 (0.64, 0.76)***
	≥35	133	(2.9)	195	4.0	48.9 (42.5, 56.3)	0.66 (0.56, 0.79)***
	Not married	859					
Socioeconomic class at 1960 census (household)	Non-manual	2761	(51.9)	4689	82.7	56.7 (55.1, 58.3)	0.81 (0.77, 0.84)***
	Manual	1882	(35.4)	3958	56.4	70.2 (68.0, 72.4)	1
	Self-employed	676	(12.7)	1561	20.2	77.1 (73.3, 81.0)	1.10 (1.04, 1.16)**
	Missing	186					
Level of education (own)	Elementary school	5231	(95.0)	9953	156.7	63.5 (62.3, 64.8)	1
	Higher	273	(5.0)	518	8.2	63.4 (58.1, 69.0)	1.00 (0.91, 1.09)
	Missing	1					
Occupation at 1960 census	In paid work	1944	(36.8)	2514	58.2	43.2 (41.5, 44.9)	0.56 (0.53, 0.59)***
	Not in work	3338	(63.2)	7715	100	77.1 (75.4, 78.9)	1
	Missing	223			58.2		
Fertility							
Age at first birth (if children)	<20	561	(12.4)	1692	16.8	100.6 (95.6, 105.5)	1.21 (1.15, 1.27)***
	20-24	1885	(41.5)	4706	56.5	83.3 (81.0, 85.7)	1
	25-29	1442	(31.8)	3049	43.2	70.5 (68.1, 73.1)	0.85 (0.82, 0.87)***
	30-34	508	(11.2)	836	15.2	54.9 (52.3, 58.7)	0.66 (0.63, 0.69)***
	≥35	145	(3.2)	188	4.3	43.3 (37.6, 50.0)	0.52 (0.48, 0.56)***
	No births	963					

***p <0.001 **p <0.01 ***p<0.05

Table 5.6: General fertility rates and age-specific fertility rates for all women aged 15-44 by their birthweight category

Age band	Low birthweight (<2500g)			Normal birthweight (≥ 2500g)			Unadjusted Fertility Rate Ratio	Adjusted Fertility Rate Ratio*
	No. of live births n	Fertile person-time (1000 py)	Fertility Rate (95% CI)	No. of live births	Fertile person-time (1000 py)	Fertility Rate (95% CI)	(95% CI)	(95% CI)
All	385	6.5	59.3 (53.6, 65.5)	10071	158.2	63.6 (62.4, 64.9)	0.93 (0.84, 1.03)	0.92 (0.82, 1.04)
15 - <20	23	1.1	21.2 (14.1, 31.9)	596	26.4	22.6 (20.8, 24.4)	0.94 (0.59, 1.49)	0.88 (0.56, 1.39)
20 - <25	118	1.1	108.8 (90.8, 130.3)	2785	26.4	105.4 (101.6, 109.4)	1.03 (0.86, 1.24)	1.00 (0.84, 1.20)
25 - <30	131	1.1	120.7 (10179, 143.3)	3404	26.4	128.9 (124.6, 133.3)	0.94 (0.79, 1.11)	0.94 (0.79, 1.11)
30 - <35	76	1.1	70.1 (56.0, 87.8)	2182	26.4	82.6 (79.2, 86.2)	0.85 (0.68, 1.06)	0.86 (0.68, 1.07)
35 - <40	29	1.1	26.8 (18.7, 38.6)	910	26.4	34.5 (32.4, 36.8)	0.78 (0.54, 1.11)	0.79 (0.55, 1.13)
40 - <45	8	1.1	7.4 (3.7, 14.8)	194	26.3	7.4 (6.4, 8.5)	1.00 (0.50, 2.01)	1.03 (0.51, 2.07)

*adjusted for effect of birth cohort and socioeconomic position at birth

Table 5.7: General fertility rates and age-specific fertility rates for all women aged 15-44 by their gestation category

	Preterm (<37 weeks)			Term (≥ 37 weeks)				
Age band	No. of live births n	Fertile person-time (1000 py)	Fertility Rate (95% CI)	No. of live births	Fertile person-time (1000 py)	Fertility Rate (95% CI)	Unadjusted Fertility Rate Ratio (95% CI)	Adjusted Fertility Rate Ratio* (95% CI)
All	659	10.8	60.9 (56.4, 65.7)	9502	149.3	63.6 (62.4, 64.9)	0.96 (0.88, 1.04)	0.96 (0.88, 1.03)
15 - <20	34	1.8	18.8 (13.5, 26.4)	571	24.9	22.9 (21.1, 24.9)	0.82 (0.58, 1.17)	0.77 (0.54, 1.09)
20 - <25	184	1.8	101.9 (88.2, 117.8)	2630	24.9	105.5 (101.5, 109.6)	0.97 (0.84, 1.12)	0.94 (0.81, 1.08)
25 - <30	229	1.8	126.9 (111.5, 144.4)	3212	24.9	128.8 (124.5, 133.4)	0.98 (0.87, 1.12)	0.99 (0.87, 1.12)
30 - <35	138	1.8	76.4 (64.7, 90.3)	2057	24.9	82.5 (79.0, 86.2)	0.93 (0.79, 1.09)	0.95 (0.81, 1.10)
35 - <40	64	1.8	35.5 (27.7, 45.3)	847	24.9	34.1 (31.8, 36.4)	1.04 (0.80, 1.35)	1.07 (0.82, 1.39)
40 - <45	10	1.8	5.6 (3.0, 10.3)	185	24.8	7.5 (6.5, 8.6)	0.75 (0.40, 1.40)	0.77 (0.41, 1.44)

*adjusted for effect of birth cohort and socioeconomic position at birth

Table 5.8: General fertility rates and age-specific fertility rates for all women aged 15-44 by their category of birthweight for gestational age

	<10th centile weight for gestational age			≥10th centile weight for gestational age				
Age band	No. of live births n	Fertile person-time (1000 py)	Fertility Rate (95% CI)	No. of live births	Fertile person-time (1000 py)	Fertility Rate (95% CI)	Unadjusted Fertility Rate Ratio (95% CI)	Adjusted Fertility Rate Ratio* (95% CI)
All	832	13.2	63.0 (58.9, 67.4)	9314	146.8	63.5 (62.2, 64.8)	0.99 (0.93, 1.07)	0.99 (0.92, 1.06)
15 - <20	62	2.2	28.1 (21.9, 36.1)	543	24.5	22.2 (20.4, 24.1)	1.27 (0.96, 1.68)	1.21 (0.92, 1.59)
20 - <25	253	2.2	114.7 (101.4, 129.8)	2556	24.5	104.3 (100.4, 108.5)	1.10 (0.97, 1.25)	1.06 (0.94, 1.21)
25 - <30	266	2.2	120.6 (107.0, 136.0)	3170	24.5	129.4 (125.0, 134.0)	0.93 (0.83, 1.04)	0.94 (0.84, 1.05)
30 - <35	164	2.2	74.4 (63.8, 86.7)	2028	24.5	82.8 (79.3, 86.5)	0.90 (0.77, 1.04)	0.91 (0.78, 1.06)
35 - <40	70	2.2	31.9 (25.2, 40.3)	839	24.4	34.3 (32.1, 36.7)	0.93 (0.72, 1.19)	0.95 (0.74, 1.22)
40 - <45	17	2.2	7.8 (4.8, 12.5)	178	24.3	7.3 (6.3, 8.5)	1.06 (0.63, 1.78)	1.11 (0.66, 1.86)

*adjusted for effect of birth cohort and socioeconomic position at birth

Table 5.9: General fertility rates and age-specific fertility rates for all women aged 15-44 by their ponderal index quintile

	Low ponderal index (lowest quintile)			2-5th quintile for ponderal index				
Age band	No. of live births n	Fertile person-time (1000 py)	Fertility Rate (95% CI)	No. of live births	Fertile person-time (1000 py)	Fertility Rate (95% CI)	Unadjusted Fertility Rate Ratio (95% CI)	Adjusted Fertility Rate Ratio* (95% CI)
All	1671	27	61.8 (58.9, 64.8)	8756	137.2	63.2 (62.5, 65.2)	0.97 (0.92, 1.02)	0.99 (0.94, 1.04)
15 - <20	96	4.5	21.3 (17.4, 26.0)	522	22.9	22.8 (20.9, 24.8)	0.93 (0.74, 1.18)	1.04 (0.82, 1.31)
20 - <25	421	4.5	93.3 (84.8, 102.7)	2477	22.9	108.1 (103.9, 112.5)	0.86 (0.78, 0.96)	0.92 (0.83, 1.02)
25 - <30	571	4.5	126.6 (116.6, 137.4)	2955	22.9	129.0 (124.4, 133.7)	0.98 (0.90, 1.07)	0.98 (0.90, 1.07)
30 - <35	390	4.5	86.5 (78.3, 95.5)	1862	22.9	81.3 (77.7, 85.0)	1.06 (0.96, 1.18)	1.07 (0.96. 1.19)
35 - <40	155	4.5	34.4 (29.4, 40.3)	779	22.8	34.1 (31.8, 36.6)	1.01 (0.84, 1.20)	0.99 (0.83, 1.19)
40 - <45	38	4.5	8.4 (6.1, 11.6)	161	22.7	7.1 (6.1, 8.3)	1.19 (0.83, 1.72)	1.11 (0.76, 1.61)

*adjusted for effect of birth cohort and socioeconomic position at birth

Figure 5.6: Flowchart of sample 2

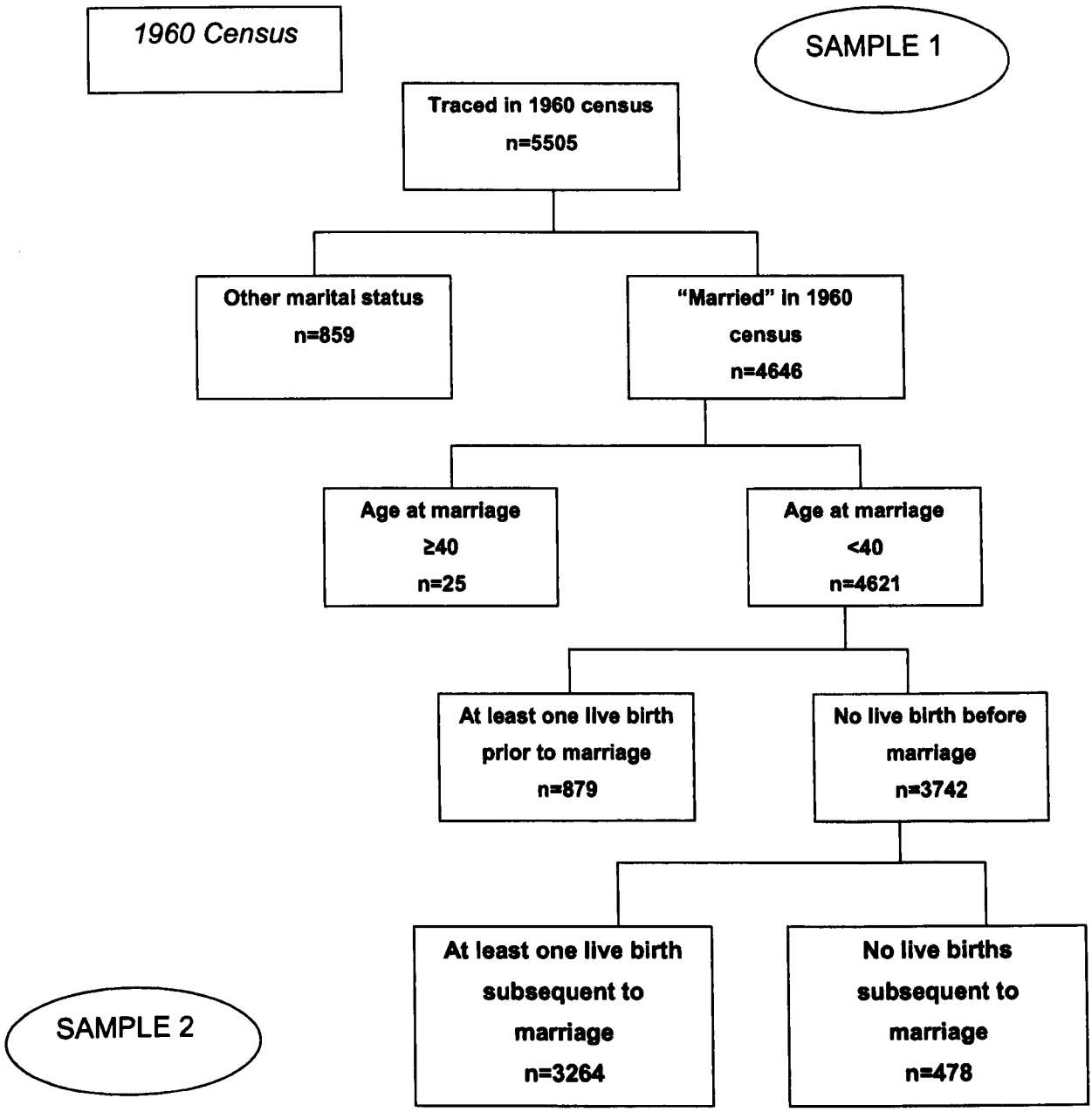


Figure 5.7: Exclusions for sample 2

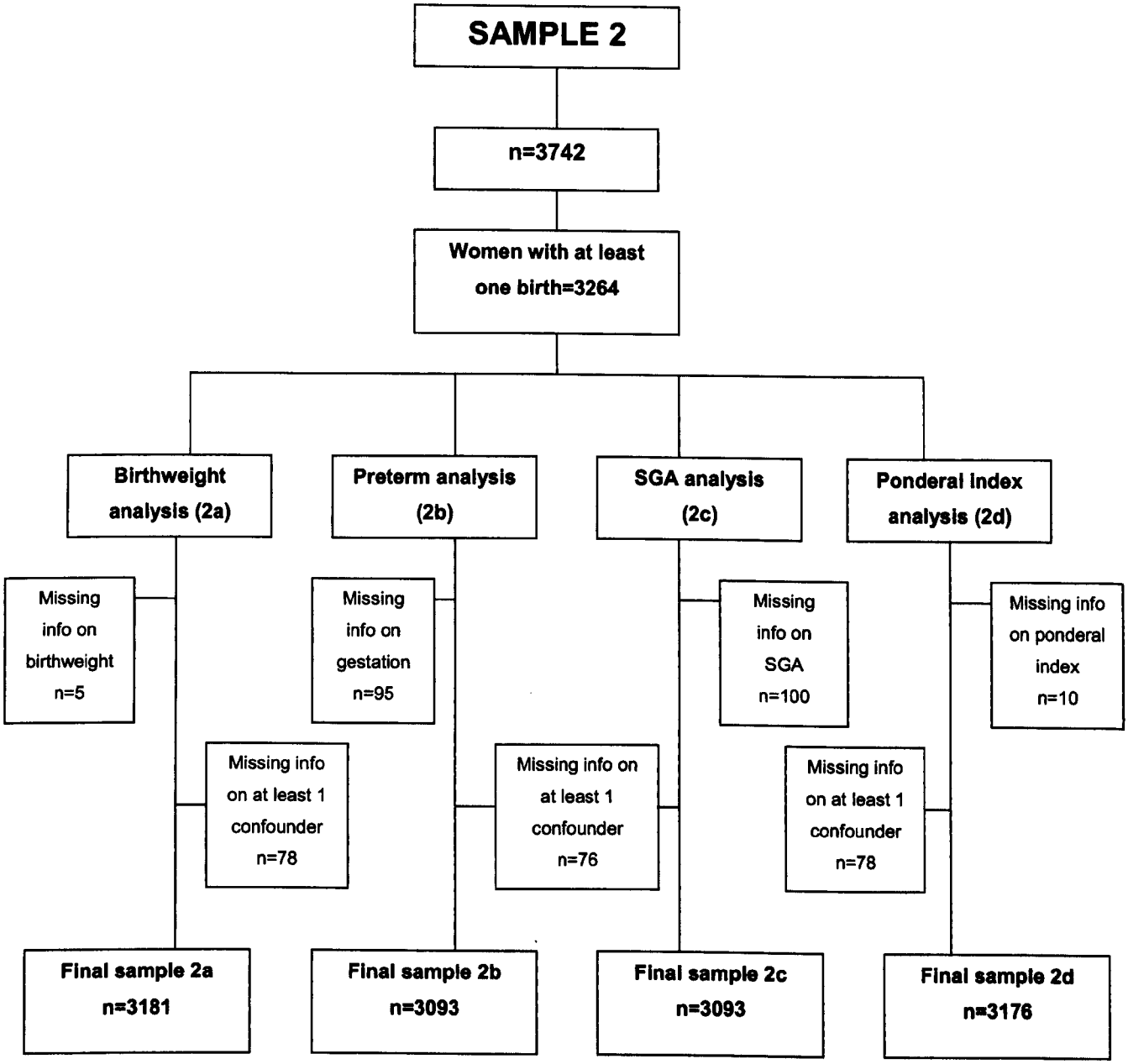


Figure 5.8: Proportion of women experiencing first live birth by time since marriage

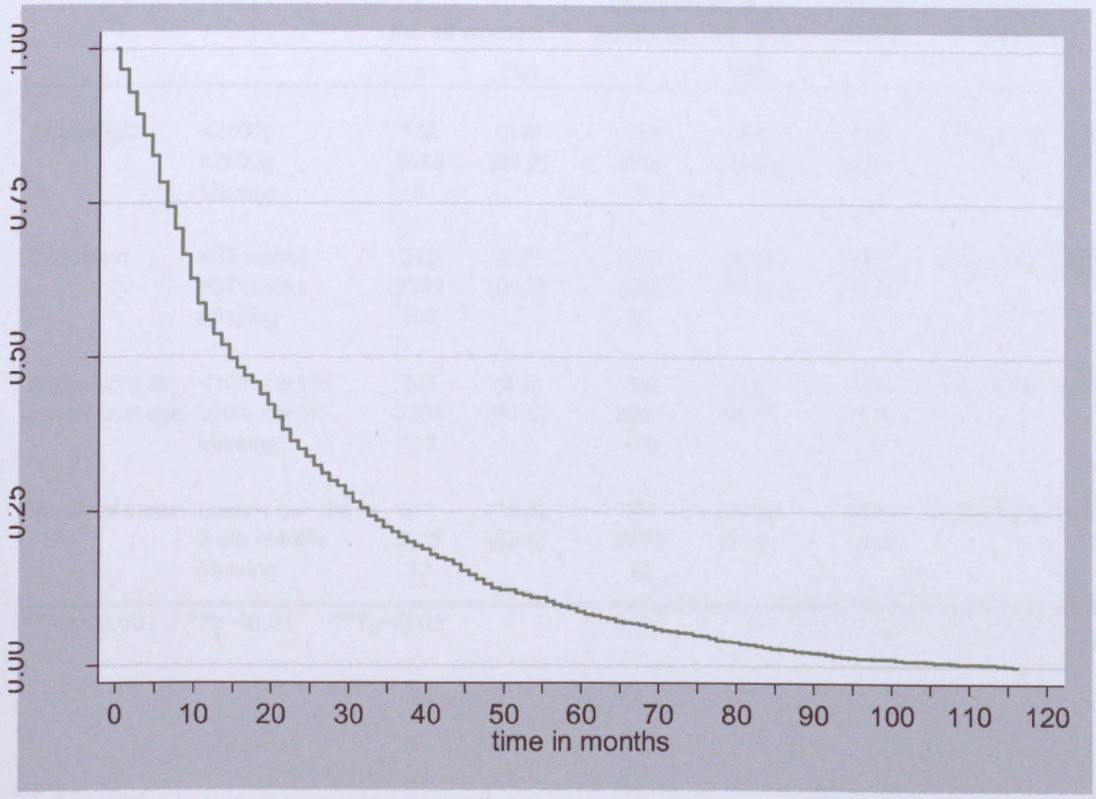


Table 5.10: Median time to first live birth and fecundability ratios according to early life factors

		No. of women		No. of women experiencing at least one live birth		Median TTFLB (mths)	Crude Fecundability Ratio (95% CI)
		n	(%)	n	(%)		
Birthweight	<2500g	142	(3.8)	125	(3.8)	13.5	0.93 (0.78, 1.12)
	≥2500g	3595	(96.2)	3134	(96.2)	15.5	1
	Missing	5		5			
Gestation	<37 weeks	242	(8.7)	212	(8.1)	18.5	0.93 (0.81, 1.07)
	≥37 weeks	3392	(91.3)	2957	(91.9)	15.5	1
	Missing	108		95			
Birthweight for gestational age	<10th centile	298	(8.2)	254	(8.0)	13.5	1.05 (0.93, 1.20)
	≥10th centile	3331	(91.8)	2910	(92.0)	15.5	1
	Missing	113		100			
Ponderal index	Lowest quintile	615	(16.5)	537	(16.5)	18.5	0.93 (0.85, 1.02)
	2-5th quintile	3115	(83.5)	2717	(83.5)	14.5	1
	Missing	12		10			

***p <0.001 **p <0.01 ***p<0.05

Table 5.11: Median time to first live birth and fecundability ratios according to sociodemographic characteristics at birth

		No. of women		No. of women experiencing at least one live birth		Median TTFLB (mths)	Crude Fecundability Ratio (95% CI)
		n	(%)	n	(%)		
Year of birth	1915-1919	984	(26.3)	832	(25.5)	21.5	1
	1920-1924	1279	(34.2)	1109	(34.0)	16.5	1.11 (1.01, 1.20)*
	1925-1929	1479	(39.5)	1323	(40.5)	11.5	1.29 (1.18, 1.41)***
Age of woman's mother at her birth	<20	202	(5.4)	180	(5.5)	16.5	0.95 (0.81, 1.08)
	20-29	2044	(54.7)	1772	(54.2)	15.5	1
	30-39	1269	(33.9)	1109	(33.9)	15.5	1.00 (0.93, 1.08)
	≥40	225	(6.0)	210	(6.4)	14.5	1.08 (0.94, 1.25)
	Missing	2		2			
Civil status of woman's mother at her birth	Married	3015	(80.7)	2633	(80.8)	15.5	1
	Single	687	(18.4)	597	(18.3)	14.5	1.02 (0.94, 1.12)
	Divorced/widowed	32	(0.9)	27	(0.8)	10.5	1.29 (0.89, 1.89)
	Missing	8		7			
Residence	Uppsala	1814	(48.5)	1560	(47.9)	18.6	1
	Other	1924	(51.5)	1700	(52.1)	12.5	1.18 (1.10, 1.27)***
	Missing	4		4			
Socioeconomic class at birth	higher non-manual	294	(7.9)	263	(8.1)	14.5	1.14 (1.00, 1.31)#
	medium/lower non-manual	619	(16.5)	519	(15.9)	15.5	1.07 (0.97, 1.19)
	farmers or self-employed	634	(16.9)	573	(17.6)	13.5	1.21 (1.09, 1.34)***
	higher manual	571	(15.3)	505	(15.5)	17.5	0.98 (0.88, 1.09)
	lower manual	1340	(35.8)	1154	(35.4)	16.6	1
	other	284	(7.6)	250	(7.7)	15.5	1.04 (0.91, 1.19)

***p <0.001 **p <0.01 ***p<0.05 #p <0.10

Table 5.12: Median time to first live birth and fecundability ratios according to adult sociodemographic characteristics

		No. of women		No. of women experiencing at least one live birth		Median TTFLB (mths)	Crude Fecundability Ratio (95% CI)
		n	(%)	n	(%)		
Age at marriage	<20	372	(9.9)	363	(11.1)	8.5	1.58 (1.39, 1.74)***
	20-24	1989	(53.2)	1829	(56.0)	16.6	1
	25-29	1040	(27.8)	866	(26.5)	18.6	0.95 (0.88, 1.03)
	30-34	282	(7.5)	177	(5.4)	15.5	1.15 (0.99, 1.34)#
	≥35	59	(1.6)	29	(0.9)	22.5	1.06 (0.73, 1.53)
Husband's age at marriage	<25	1276	(34.4)	1196	(36.7)	10.5	1.20 (1.11, 1.30)***
	25-29	1579	(42.5)	1422	(43.6)	19.5	1
	30-34	567	(15.3)	448	(13.8)	16.6	1.06 (0.96, 1.18)
	35-39	198	(5.3)	148	(4.5)	16.5	1.11 (0.94, 1.32)
	≥40	94	(2.5)	44	(1.4)	14.5	1.15 (0.85, 1.56)
	Missing	28		6			
Socioeconomic class (household)	Non-manual	1966	(52.9)	1682	(51.9)	18.5	0.83 (0.76, 0.89)***
	Manual	1213	(32.7)	1066	(32.9)	11.5	1
	Self-employed	534	(14.4)	491	(15.2)	14.5	0.87 (0.78, 0.97)**
	Missing	29		25			
Level of education (own)	Elementary school	3557	(95.1)	3092	(94.7)	15.5	1
	Higher	184	(4.9)	172	(5.3)	19.5	0.96 (0.82, 1.12)
	Missing	1		0			
Occupation	Not in work	2624	(71.7)	2438	(76.1)	16.5	1
	In paid work	1038	(28.3)	764	(23.9)	12.5	1.01 (0.93, 1.09)
	Missing	80		62			

***p <0.001 **p <0.01 ***p<0. 05 #p <0.10

Figure 5.9: Proportion conceiving first live birth by birthweight category

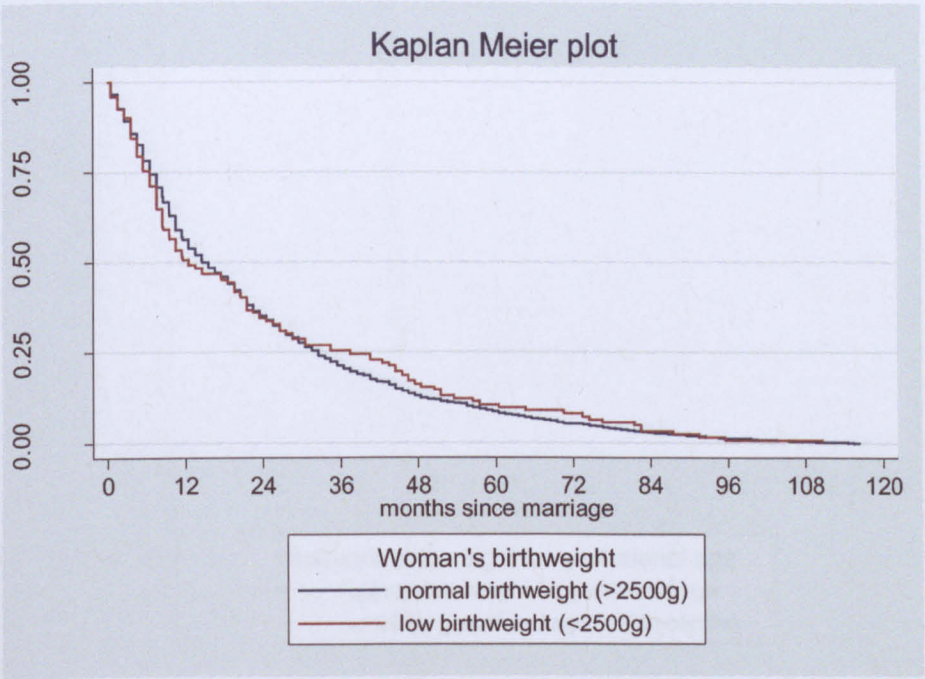


Figure 5.10: Proportion conceiving first live birth by gestation category

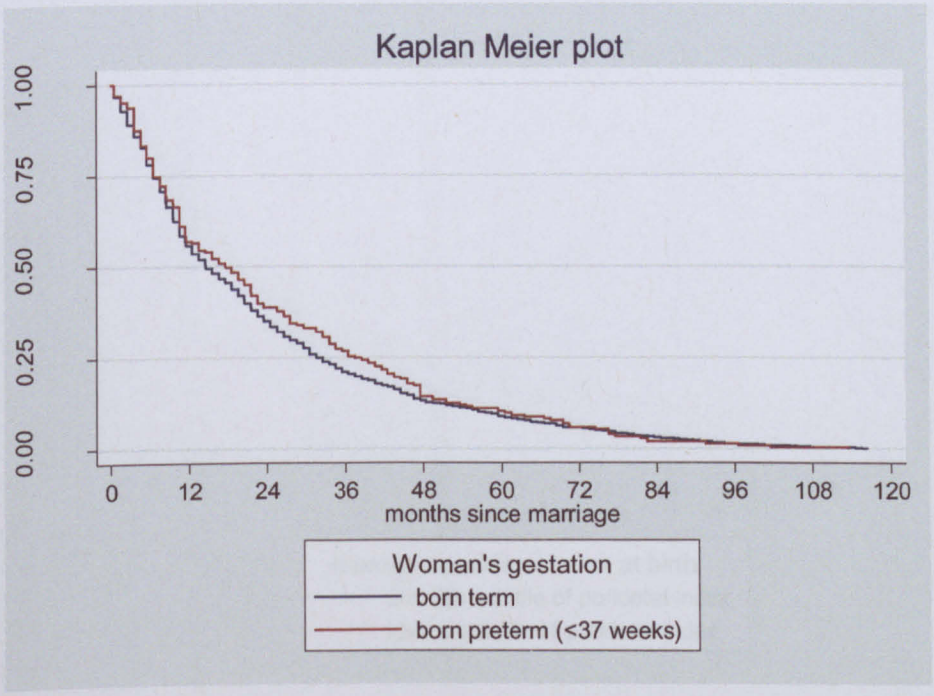


Figure 5.11: Proportion conceiving first live birth by small for gestational status

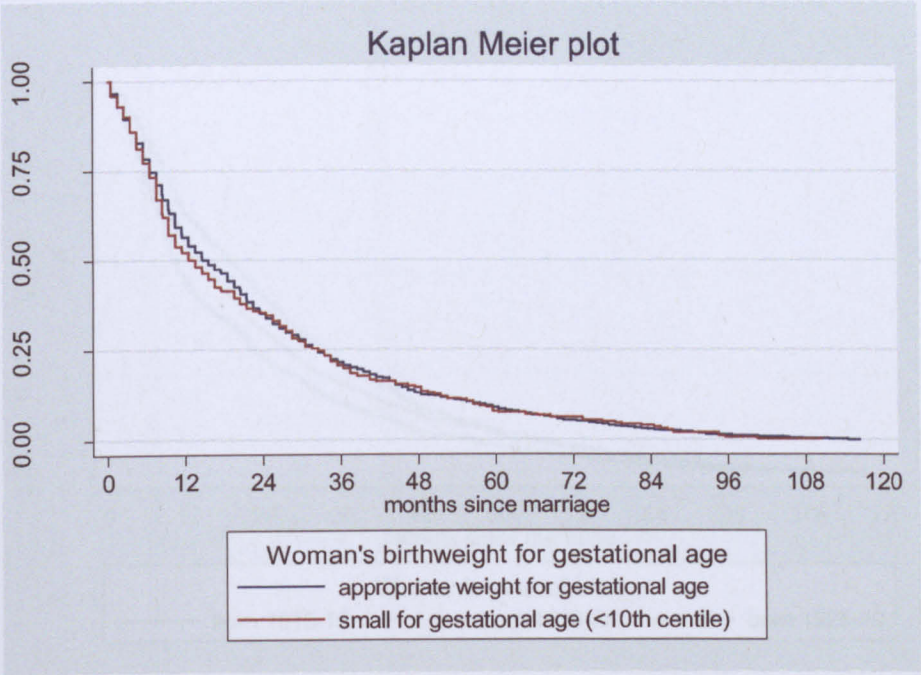


Figure 5.12: Proportion conceiving first live birth by ponderal index category

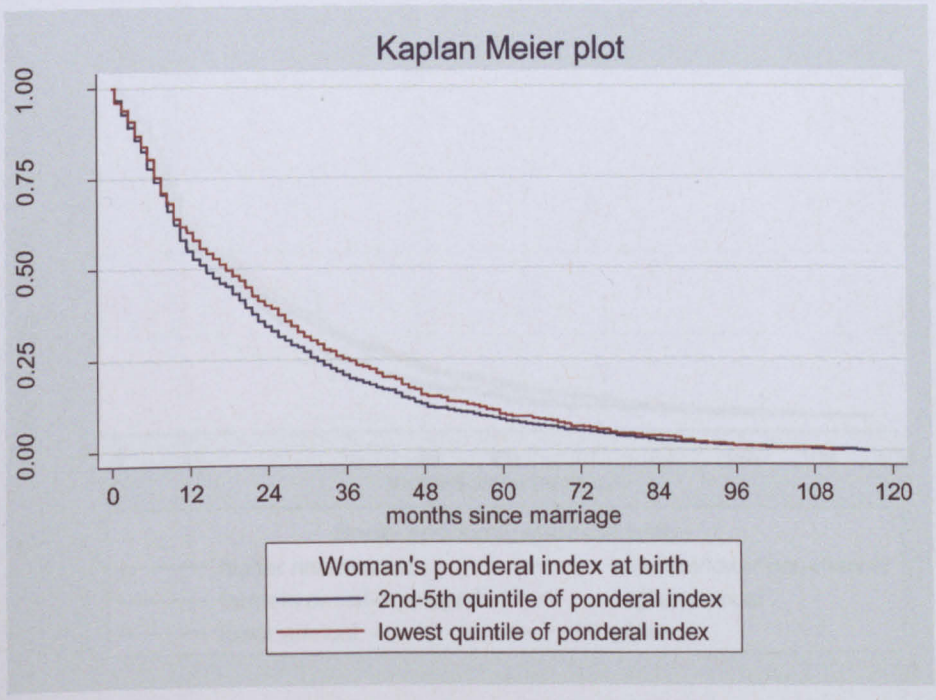


Figure 5.13: Proportion conceiving first live birth by birth cohort

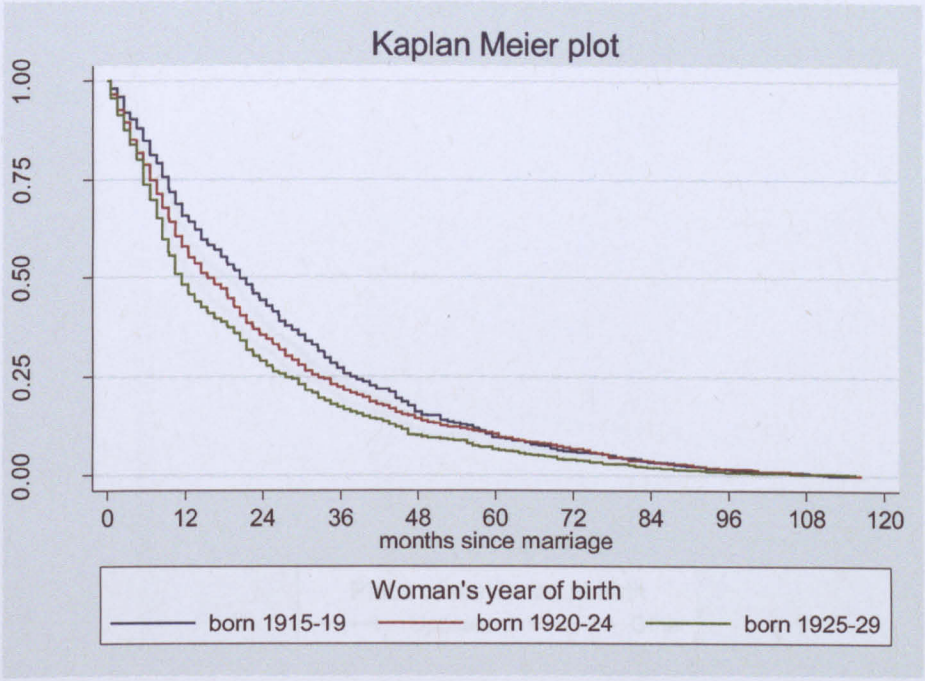


Figure 5.14: Proportion conceiving first live birth by socioeconomic group at birth

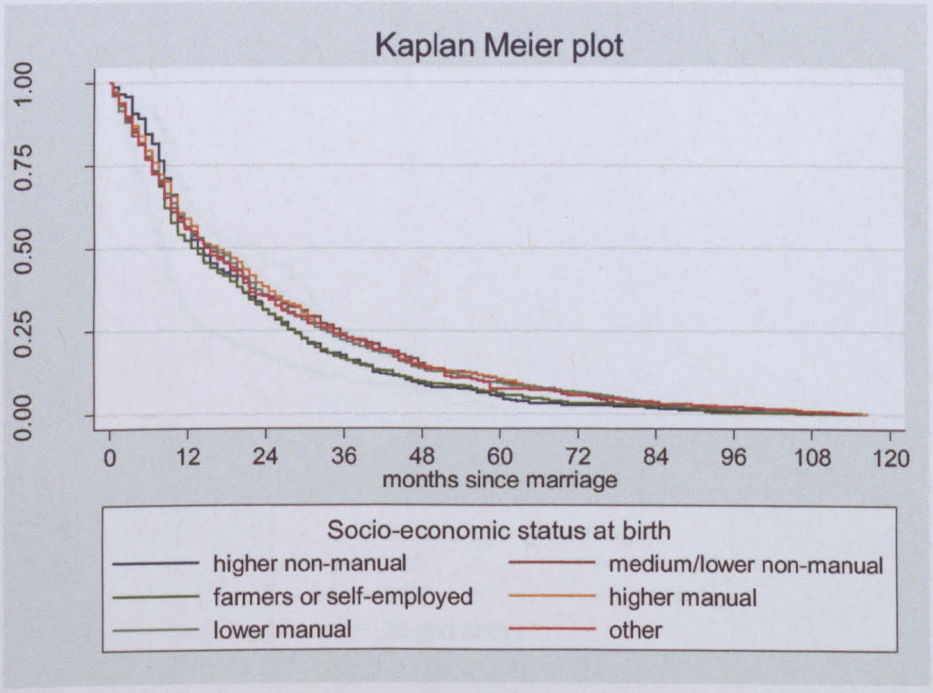


Figure 5.15: Proportion conceiving first live birth by place of birth

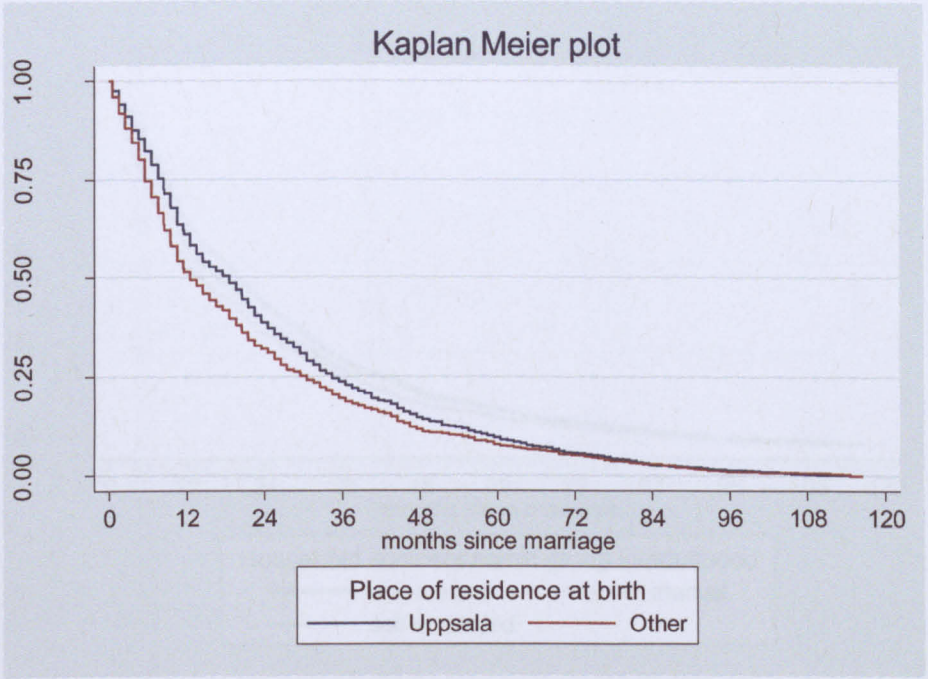


Figure 5.16: Proportion conceiving first live birth by age at marriage

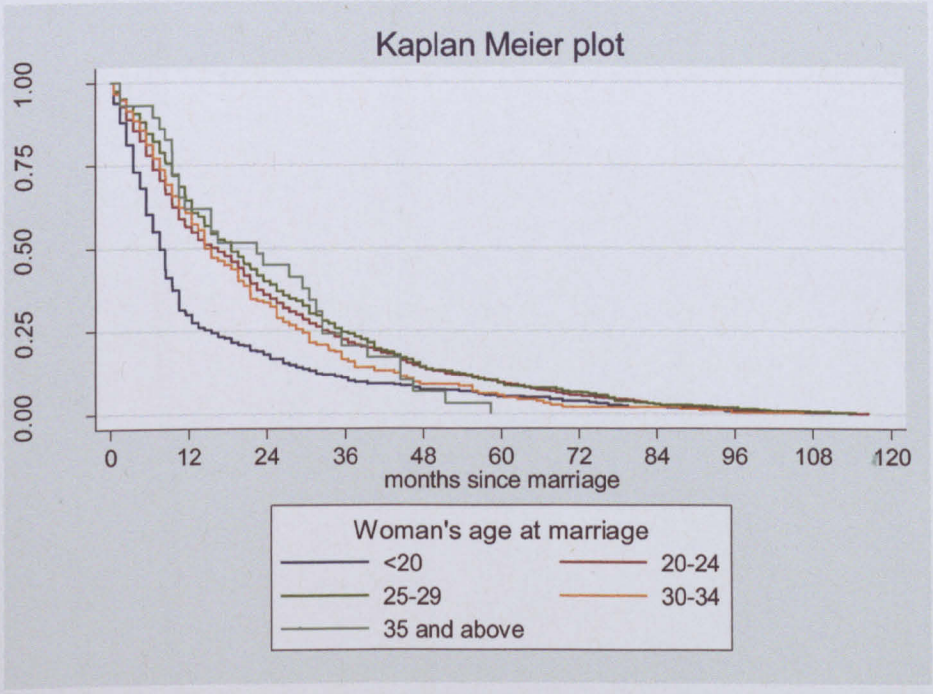


Figure 5.17: Proportion conceiving first live birth by adult socioeconomic group

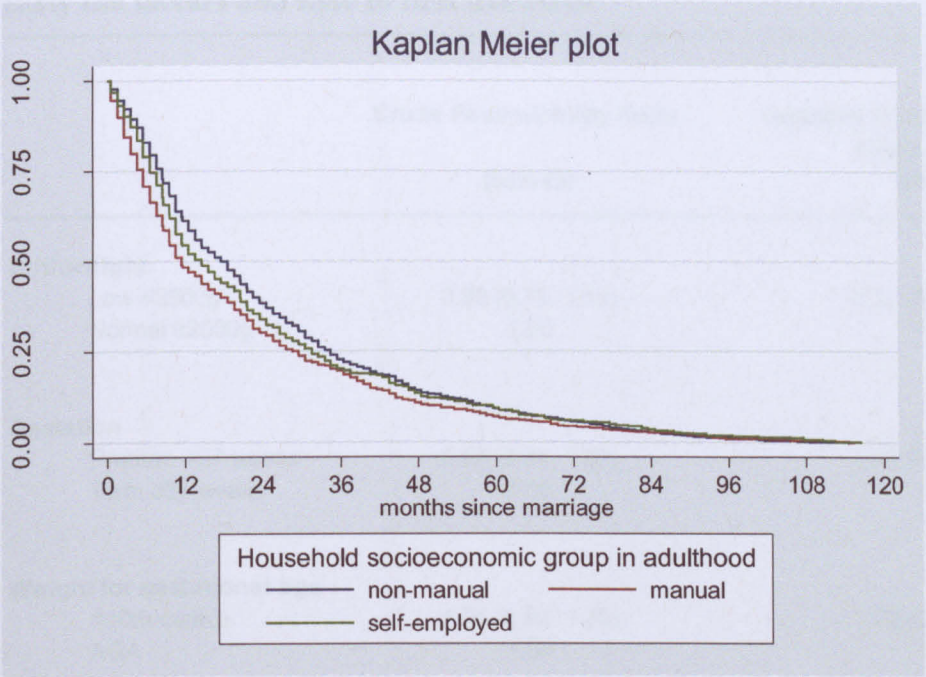


Table 5.13: Crude and adjusted fecundability ratios for the association between early life factors and time to first live birth

	Crude Fecundability Ratio (95% CI)	Adjusted Fecundability Ratio* FINAL MODEL (95% CI)
Birthweight		
Low <2500g	0.93 (0.78. 1.12)	0.92 (0.77, 1.10)
Normal ≥2500g	1.00	1.00
Gestation		
Preterm <37 weeks	0.93 (0.81, 1.07)	0.93 (0.81, 1.07)
Term ≥37 weeks	1.00	1.00
Weight for gestational age		
<10th centile	1.05 (0.93, 1.20)	1.03 (0.90, 1.17)
AGA	1.00	1.00
Ponderal Index		
Lowest quintile	0.93 (0.85, 1.02)	0.97 (0.88, 1.06)
2nd-5th quintiles	1.00	1.00

* adjusted for period of birth, socioeconomic group at birth, and age at marriage

Table 5.14: Crude fecundability ratios for the association between early life factors and time to first live birth according to different estimations of marriage date (sensitivity analysis 1)

			n	(%)	Median TTFLB	Crude Fecundability Ratio (95% CI)	p value
MARRIAGE ASSUMED JANUARY	Birthweight	<2500g	136	(3.9)	16.9	0.94 (0.80, 1.12)	0.5
		≥2500g	3379	(96.1)	19.4	1.00	
	Gestation	<37 weeks	232	(6.8)	20.9	0.95 (0.83, 1.08)	0.5
		≥37 weeks	3183	(93.2)	19.4	1.00	
marriage assumed to have taken place on 1st Jan and women excluded if their first child was born before this date	Birthweight for gestational age	<10th centile	272	(8.0)	17.4	1.04 (0.92, 1.18)	0.5
		≥10th centile	3143	(92.0)	19.4	1.00	
	Ponderal index	Lowest quintile	575	(16.4)	21.4	0.93 (0.85, 1.01)	0.1
		2-5th quintile	2935	(83.6)	18.4	1.00	
MARRIAGE ASSUMED JUNE	Birthweight	<2500g	125	(3.8)	13.5	0.93 (0.78, 1.12)	0.4
		≥2500g	3134	(96.2)	15.5	1.00	
	Gestation	<37 weeks	212	(8.1)	18.5	0.93 (0.81, 1.07)	0.3
		≥37 weeks	2957	(91.9)	15.5	1.00	
marriage assumed to have taken place on 30th Jun and women excluded if their first child was born before this date	Birthweight for gestational age	<10th centile	254	(8.0)	13.5	1.05 (0.93, 1.20)	0.4
		≥10th centile	2910	(92.0)	15.5	1.00	
	Ponderal index	Lowest quintile	537	(16.5)	18.5	0.93 (0.85, 1.02)	0.1
		2-5th quintile	2717	(83.5)	14.5	1.00	
MARRIAGE ASSUMED DECEMBER	Birthweight	<2500g	95	(3.7)	16.5	0.88 (0.72, 1.08)	0.2
		≥2500g	2463	(96.3)	15.5	1.00	
	Gestation	<37 weeks	170	(6.8)	17.4	0.93 (0.80, 1.09)	0.4
		≥37 weeks	2322	(93.2)	15.5	1.00	
marriage assumed to have taken place on 31st Dec and women excluded if their first child was born before this date	Birthweight for gestational age	<10th centile	197	(7.9)	14.4	1.05 (0.91, 1.21)	0.5
		≥10th centile	2295	(92.1)	15.5	1.00	
	Ponderal index	Lowest quintile	432	(16.9)	18.4	0.94 (0.85, 1.04)	0.3
		2-5th quintile	2122	(83.1)	15.5	1.00	

Table 5.15: Crude odds ratios for the association between early life factors and time to first live birth categorised as a binary variable (sensitivity analysis 2)

		No. of women		First live birth the year after the year of marriage		First live birth two or more years after the year of marriage		Crude odds ratio (95% CI)
		n	(%) column	n	(%) row	n	(%) row	
Birthweight	**<2500g**	95	(3.7)	37	(38.9)	58	(61.1)	1.07 (0.70, 1.63)
	≥2500g	2463	(96.3)	999	(40.6)	1464	(59.4)	1
	Missing	4		3		1		
Gestation	**<37 weeks**	170	(6.8)	63	(37.1)	107	(62.9)	1.17 (0.85, 1.62)
	≥37 weeks	2322	(93.2)	948	(40.8)	1374	(59.2)	1
	Missing	70		28		42		
Birthweight for gestational age	**<10th centile**	197	(7.9)	90	(45.7)	107	(54.3)	0.79 (0.59, 1.06)
	≥10th centile	2291	(92.1)	918	(40.1)	1373	(59.9)	1
	Missing	74		31		43		
Ponderal index	**Lowest quintile**	432	(16.9)	163	(37.7)	269	(62.3)	1.15 (0.93, 1.42)
	2-5th quintile	2122	(83.1)	872	(41.1)	1250	(58.9)	1
	Missing	8		4		4		

Chapter 6: Uppsala Birth Cohort Study Multigen - Discussion

This chapter provides a summary of the results from the analyses of UBCoS data presented in the preceding chapter. The results are discussed in context, with reference to existing literature and in view of the strengths and limitations of the data source and analysis strategies.

6.1 OVERVIEW OF MAIN FINDINGS

These analyses are based on a retrospective cohort study which originated with the extraction of the obstetric records of 14,611 births occurring in Uppsala, Sweden during the period 1915-1929. The sample used in the analyses reported here is based on the 5505 women who fulfilled the following criteria: liveborn, survived to adulthood, were alive and resident in Sweden in 1947, and linked to the 1960 census. Using the data collected from obstetric records, the social and reproductive careers of these women have been followed up using linkage to other routine data sources. The focus of this work has been an investigation of the association between early life factors, specifically markers of *in utero* growth, and later fertility in this population of women. Recognising the limits of the data available, fertility in adulthood was defined using two separate approaches: general and age-specific fertility rates, and time to first live birth. Results from the reported analyses suggest there is no clear evidence to support an association between early life factors and later fertility.

6.1.1 Effect of early life factors on fertility rates

Four markers of *in utero* growth – birthweight, gestation, birthweight for gestational age, and ponderal index – were investigated with regard to their effect on general and age specific fertility rates among women born 1915-29. Age-specific fertility rates were calculated to represent the fertility experience of the cohort over the specified age range. Fertility rates varied considerably according to age ranges, but only minor fluctuations were observed when adjusted age-specific rates were compared according to markers of *in utero* growth. Measures of effect were consistently less than 1, but confidence

intervals spanned 1, providing little evidence of an underlying trend. In conclusion, these analyses did not reveal any differences in fertility rates according to proxy measures of *in utero* growth.

6.1.2 Effect of early life factors on time to first live birth

Time to first live birth was investigated among a sample of women who reported their civil status as 'married' in the 1960 census. Time to first live birth was calculated as the period between the date of their marriage (estimated as the mid-year point of the reported year) and the birth of their first liveborn child. The effect of these same four markers of *in utero* growth (birthweight, gestation, birthweight for gestational age and ponderal index) on time to first live birth was considered. After adjusting for possible confounding, there was no clear evidence of an association between any of these factors and time to first live birth was detected. Three out of four point estimates for early life factors were below 1, but the confidence intervals for these measures of effect robustly spanned 1. These findings were confirmed by two separate sensitivity analyses, which support the conclusions from the main analysis.

6.2 CONSISTENCY WITH EXISTING LITERATURE

As identified in the background section of this thesis, there is only sparse published evidence on the association between early life factors such as *in utero* growth and fertility in adult women. This paucity of data provides both challenges and opportunities for those conducting work in this area.

A brief analysis of UBCoS data looking at the relationship between being born preterm or low birth weight for gestational age and childlessness in adult women reported no significant association.[226] A further relevant analysis of UBCoS data looked at the relationship between early life factors and subsequent reproductive success, measured as the overall number of children and/or number of grandchildren born to a G1 woman.[227] The authors of this study report that certain birth characteristics were associated with long-term reproductive success, namely a higher birthweight for gestational age, term birth and a younger maternal age, all of which were associated with an increased number of descendents. Marital status appeared to mediate some of

these effects, with the probability of marriage determined by many of the biological factors under study.

Several other studies have provided some evidence of a link between early life factors and the probability of giving birth. One US study reported that women born very low birthweight (VLBW) had lower rates of both pregnancy and livebirth,[231] and a Norwegian study found that women who were born preterm had a lower probability of overall reproduction.[230] The results from a Swedish study were less clear cut. Women born VLBW had a reduced probability of giving birth, but those born SGA appeared more likely to have given birth.[229]

A few studies have looked at exposure to famine *in utero* as a proxy of *in utero* growth; such studies have reported inconsistent findings with respect to later fertility in women.[233-234] The relevance of these studies to the data analyses here is questionable; the severe undernutrition observed in famine circumstances is unlikely to be any way equivalent to the more commonly observed restricted growth observed in generally well nourished populations.

Despite the popularity of TTP studies, such approaches have been used rarely in the investigation of early life exposures such as *in utero* growth. This is probably due in part to the difficulty of sourcing reliable data on early life exposures in addition to accurate information on TTP. One Danish study used national birth cohort data to ascertain whether birthweight was associated with delayed conception (TTP of 12 months or more). In this study, both women who reported a low birthweight (≤2500g for term births and ≤1500g for preterm births) and those who reported a high birthweight (≥4500g for term births and ≥3500g for preterm births) appeared to be at increased risk of delayed conception. However, the authors note that these associations seem to be mediated by BMI in adulthood, with the association between low birthweight and delayed conception strongest in those with a BMI <25 in adulthood.[228] A recent French study found no evidence for a link between being born SGA and fertility in adulthood, measured either as TTP or the monthly probability of conception.[232]

Overall, the existing literature seems to report no clear trends with respect to the link between early life factors and later fertility in women. The results reported in the present analyses appear to add to those existing studies which fail to support an association between markers of *in utero* growth and fertility in women.

6.3 STRENGTHS AND LIMITATIONS

6.3.1 Representativeness of sample

The Uppsala birth cohort study is often described as a population-based study, though strictly speaking it is in fact a hospital-based cohort. It is therefore legitimate to wonder how this cohort differs from one that is truly 'population-based'. Sweden was one of the first industrialised countries in which hospital births replaced home births in terms of popularity, with the greatest shift from home to hospital observed during the 1920s and 1930s.[345] Nationwide, only 10% of births took place in hospital in 1915, rising to 18% in 1930.[345] However, Uppsala is located in one of the few regions where hospital births were particularly prevalent, with less than 40% of births in taking place at home by 1934.[345]There is clear evidence to suggest that the majority of women residing in the local area who gave birth during the study period (1915-1929) did so in Uppsala Academic hospital; 75% and 50% of births occurring in Uppsala city and local parishes respectively took place in the hospital at this time.[330] But did the births that took place outside the hospital differ in any way from the hospital births? One of the original aims of maternity hospitals was to provide unmarried mothers with a place of delivery. Statistics do confirm that a higher proportion of UBCoS births were to unmarried women compared to local (Uppsala) and national figures at that time (Figure A.1.1, Appendix 1). However, statistics show that the within-cohort infant mortality rate does not differ markedly from local and national rates (Figure A.1.2, Appendix 1). So in summary, unmarried women (who almost certainly occupied lower socioeconomic positions in society) were over-represented in the cohort, but overall indicators of infant mortality were similar to those observed among the rest of the population.

6.3.2 Data quality, completeness and coverage

Many epidemiological studies rely on self-reported data on perinatal factors, the validity of such information is controversial.[346-348] UBCoS Multigen is based on data abstracted directly from obstetric records and is thus can be considered a prospective study in this context.

The high quality nature of the original birth cohort data is complemented by the near complete follow-up of original UBCoS participants. Only women who died or emigrated from Sweden were unable to be followed up. Right censoring (a common problem with TTP studies) should be minimal as all women (other than the small number who died or emigrated) were followed up until 2002, at which point all G1 women were well beyond their reproductive years.

The linkage to other national data sources achieved as part of the establishment of UBCoS Multigen is impressive, and has enabled data collection on a wide range of biological, social, environmental and educational indicators, collected prospectively. This data linkage is a crucial feature of the analyses reported here, enabling the linking of obstetric and sociodemographic data collected at birth, to adult sociodemographic information and family structure.

6.3.3 Variable measurement

Early life factors

The exposures variables in the analyses were all chosen as they represent early life factors, or more specifically, markers of *in utero* growth. Measurements of size at birth are known to be at best a crude proxy of *in utero* growth. Nevertheless, they are the best available markers we have access to and have been used in countless studies investigating the link between early life factors and adult outcomes. The sheer weight of evidence supporting an association between these markers and later health outcomes can be considered evidence of their usefulness in epidemiological studies.

In the analyses reported here, birthweight was used as a binary variable with <2500g considered low birthweight and any weight over this threshold considered 'normal'. This measure does not take into account gestation and therefore does not distinguish

between infants born early but at an appropriate weight, and those born at term with *in utero* growth retardation. In retrospect, it may have been useful to look at infants born at a higher than usual birthweight; commonly thresholds of >4000g or >4500g are used for this purpose. However, although there is some evidence of a link between higher birthweight and adverse outcomes in adulthood, this is not attributable to impaired fetal growth but instead may represent some alternative mechanism of disrupted development *in utero*. Some consider birthweight to be a particularly controversial marker of *in utero* growth. In particular, Wilcox has casted doubt on the use of low birthweight as a category, suggesting it is uninformative and unreliable as a predictor of health outcomes. Following work on the use of low birthweight as a predictor of infant mortality, he argues that there is no evidence of a causal link, suggesting this has implications for the wider hypothesis that links low birthweight and other crude measures of fetal growth to health outcomes in adulthood.[349]

Small for gestational age (SGA) was the second marker of *in utero* growth used in the analyses reported here. SGA is considered to be a crude measure of intrauterine growth retardation (IUGR) and has the advantage of taking into account gestational age. It is regarded as an indicator of symmetrical growth retardation. Weight for gestational age is calculated by creating cohort-specific centiles or by applying an external centile distribution. Due to the large number of births included in the UBCoS dataset and the fact that contemporary birthweight distributions are likely to differ markedly from births taking place nearly a century ago it was considered preferable to create a cohort-specific centile distribution. A variety of different thresholds are used to classify SGA; a percentage cut-off of 10% is the most commonly used and was chosen for use in the analyses reported here. With any cut-off there involves the potential for misclassification. The use of percentile distributions to classify intrauterine growth retardation has been criticised on two fronts. Firstly, it has been argued that if an external factor influences birth weights across the whole distribution in a particular population, it makes no sense to single out the smallest 10% infants.[350] Secondly, some have casted doubt on the reliability of percentile distributions to define IUGR, suggesting that they correspond poorly to clinical markers of fetal growth.[351] Nevertheless, the use of measures of birthweight adjusted for gestational age remain

useful epidemiological indicators and many consider them more informative than crude birthweight alone.

Strictly speaking, gestation is not a measure of size at birth, but can be considered a proxy for *in utero* development as infants born before term may experience premature termination of the usual process of organ growth and development. However, it is a very crude measure of *in utero* development and in particular infants born near term (34-37 weeks) are usually healthy and well developed. The highest risk of adverse outcome is likely to be in infants born very preterm. In the sample used in these analyses, infants born at a gestation of below 30 weeks were excluded, and very few were born before 35 weeks. Gestation was calculated using the reported date of the woman's last menstrual period. This is an established method of assessing gestation, although contemporary studies tend to use ultrasound measurements to more accurately define gestation, a method clearly not applicable to this early-mid 20th century born sample.

Ponderal index is a measure of thinness at birth. As a measure of body proportionality in relation to weight and length, it is considered to be a sensitive method of diagnosing infants with asymmetric growth retardation. Infants with symmetrical growth retardation have normal ponderal index values and instead are identified through assessment of weight for gestational age.

Fertility

The fertility rates reported in these analyses were calculated using the number of biological children born to G1 women, with these data taken from the linkage to routine birth registers and therefore likely to be near complete. Previous studies have used general and age-specific fertility rates to summarise the crude fertility experience of women according to a number of exposures.[26-27, 352] This approach is commonly used in demography and is recognised as a useful way to investigate differences in fertility experiences.

In the second set of analyses reported here, time to first live birth was used as a proxy for time to pregnancy (TTP). Extensive literature supporting the use of TTP as a measure of fertility in populations has been discussed in Chapter 3.

In the UBCoS Multigen data, there was no accurate information on either the start or end-point of the TTP period. The start of exposure to pregnancy was estimated as beginning at the time of marriage. The date of conception was unavailable, and the lack of information on gestational age (G2 birth) meant this could not be derived. Instead, date of birth was taken as the endpoint. A number of previous historical studies have successfully estimated TTP from the interval between marriage and first birth in this way.[23-24]

Calculating the TTP as the interval between (estimated) marriage date and the birth of the first liveborn infant rests on a number of assumptions. We assumed that the majority of women at this time would marry and would do so with the intention of starting a family, in line with prevailing socio-cultural values of the period. Although Sweden has a long tradition of non-married cohabitation, this was rare at this time with only one percent of all cohabitating couples in 1960 estimated to be unmarried.[353] We assumed that in our restricted sample (those marrying with no births before marriage) that marriage signalled the beginning of exposure to pregnancy. Our final assumption was that once married, the majority of couples were likely to practice 'natural fertility'. High quality data on the use of birth control in Sweden during the early-mid twentieth century is difficult to source. Information and instruction on birth control was forbidden by law to some degree until 1938.[354] Oral contraceptives and the IUD were not available until the mid 1960s, though induced abortion was first legalised in Sweden in 1938 in very limited circumstances (the law was augmented in 1946, 1963 and 1974 to widen the circumstances in which abortion was legal). Despite the religious taboos and prohibitive laws, there is evidence that 'family limitation' was practiced in Sweden to some degree from the late 19th century onwards.[354] This may have implications for the method of estimating time to first live birth, with couples possibly practicing natural forms of fertility control. However, there is no reason to suspect that the use of fertility control would differ according to early life factors. Therefore any effect on the observed results would most likely be due to non-differential misclassification.

We estimated that the first pregnancy conceived by the G1 woman was equivalent to the first pregnancy ending in a live birth. The multigenerational register only provided

information on liveborn infants born to G1 women, so information on pregnancies ending in an adverse outcome such as fetal death were unavailable. Therefore, the TTP of women experiencing an adverse outcome in their first pregnancy would be artificially inflated by the failure to take into account pregnancies ending in an event other than a livebirth. In this analysis TTP could be considered a proxy of the ability to achieve a pregnancy ending in a livebirth rather than a pregnancy *per se*. It could be argued that this measure of fertility is one that is of most interest. As discussed in Chapter 3, it is the ability to conceive and carry a pregnancy to live birth which is the outcome of interest to women. Some previous literature has linked early life factors with adverse pregnancy events, resulting in the possibility of exaggerating any association between early life factors and infertility in an analysis such as this. A similar effect seems unlikely in the analyses reported here given that no significant associations between early life factors and fertility were detected.

One further crucial limitation to the data was the absence of accurate information on the date of marriage. Although the year of marriage was available from the 1960 census, the day and month of marriage needed for the calculation of TTP had to be estimated; it was not possible to get these data from alternative sources. The comparison of crude results using different estimated marriage dates revealed little impact on results, with similar results observed and no difference in statistical significance. A further sensitivity analysis using year of marriage only and investigating time to first live birth as a binary outcome (first live birth the year after marriage vs. first live birth two or more years after marriage) provided similar results to the main analysis. The key issue concerning misclassification of marriage data is whether this misclassification is differential (associated with exposure) or non-differential (random). We have no reason to suspect that this misclassification was anything other than non-differential; with no plausible suggestion that date or seasonality of marriage may vary by early life factors or associated factors. However the need to estimate the data of marriage in this way may have reduced the sensitivity of the analysis, making the detection of any real association less likely. This is consistent with the established wisdom that the impact of non-differential misclassification on measures of effect is limited to biasing estimates towards the null.

A further limitation to note here is the exclusion of women according to limited information on marital status. Only women who were listed as married according to the 1960 census were included in the TTFLB sample. This had the effect of excluding not just those who were unmarried at this point and subsequently married, but also those who had previously been married and had since been divorced or widowed.

Finally, TTP only measures fertility in those who do eventually conceive. Therefore, if early life factors are associated with sterility (absolute inability to conceive) rather than reduced fertility, the analyses here would not be able to detect such an association.

Other covariates

Potential confounding factors in the analyses included sociodemographic characteristics in adulthood, measured at the 1960 census. For indicators of socioeconomic status other than achieved education, this may not accurately reflect socioeconomic position at the time of the outcome (birth) as the majority of women will have conceived their first birth before 1960.

6.3.4 Study power and chance

UBCoS Multigen is a relatively large dataset, but once specific inclusion criteria were applied, samples reduced in size greatly (n=5505 women were included in the analysis looking at fertility rates, n=3264 women were included in the analysis of time to first live birth). The initial sample size calculation was carried out for the outcome of time to first live birth, and the exposure of small for gestational age status. This calculation suggests that the analysis of this association should be sufficiently powered to detect an association. However, the numbers exposed in the analyses looking at birthweight and gestation were considerably smaller, and therefore power was more limited in these analyses. The existence of type II errors cannot be ruled out. Many of the results found in this analysis were not statistically significant, however the findings were carefully scrutinised for underlying trends that may have reached statistical significance given a larger sample size. There was no clear evidence of such trends. This suggests that the lack of an effect seen is not due to low power, but reflects a true null finding in the study population. In addition, none of the reported analyses had sufficient power in

which to detect potential effect modification, with the general recommendation that this requires a fourfold increase in sample size.[339]

6.3.5 Confounding

Attempts were made to adjust for potential confounding in the analyses and *a priori* confounders were adjusted for routinely. However, the analyses revealed little evidence of confounding by available covariates. Unmeasured confounding should be considered; the existence of other factors that may be associated with the relationship between early life factors and fertility cannot be ruled out. The analyses were obviously limited by the data available from the original birth cohort and linked registers. One possible missing confounder is growth in early infancy. In other studies looking at the association between early life factors and adult outcome, infant growth has sometimes appeared to mediate the effect of birth size.[355]

6.4 CONCLUSIONS

The dataset used in these analyses is large, with high quality data, there remain some important limitations. These primarily relate to the validity of the indicators of fertility used. Any effect of these limitations most likely resulted in a weakened ability to detect existing associations. There is no reason to suspect differential misclassification. However, the sensitivity analyses to some extent addressed these issues.

Overall, and having taken account of possible limitations, there was no robust evidence of an association between markers of *in utero* growth - namely birthweight, gestation, birthweight for gestational age, and ponderal index – and fertility, defined as either general or age-specific fertility rates, or time to first live birth among married women.

The existing literature on the relationship between early life factors and fertility in adulthood is sparse, and where it exists, findings are generally inconsistent. The results reported here add to existing knowledge and support the hypothesis of no association between markers of *in utero* growth and later fertility in women.

Chapter 7: National Women's Health Study - Data collection and Methods

This chapter details the design, methods and analysis strategy for analyses conducted on the second dataset used in this thesis: The National Women's Health Study (NWHS). NWHS was a population-based postal survey which was designed to enable the construction of a retrospective cohort of reproductive outcomes of UK women.

7.1 AIMS AND OBJECTIVES OF THE NWHS ANALYSES

The overall objectives of the NHWS analyses were as follows:

- To measure the prevalence of infertility and use of infertility treatment in the UK.
- To explore the hypothesis that one or more prior adverse reproductive events has an impact on secondary infertility in women.

7.2 STUDY DESIGN AND POPULATION

7.2.1 Study design

The National Women's Health Study (NWHS) was a large population-based postal survey designed to ascertain population-based estimates of adverse pregnancy outcome among UK women, including the prevalence of infertility and use of infertility treatment. It aimed to construct a retrospective cohort from all participants by asking them to provide a detailed reproductive history. Brief details of the study methodology are presented here, although they are described in a separate publication included in Appendix 3.[356]

7.2.2 Sampling

The NWHS randomly sampled women from the electoral registers of England, Wales, Scotland and Northern Ireland. In 2001, approximately 98% of all UK residents were on the electoral registers, and all of these were also included on the electronic version of

the register. A decision was taken to limit the study to women aged 55 and below in order to minimise bias due to poorer recall. To increase study efficiency, a probabilistic sampling technique was used which restricted the sampling frame to those women likely to be aged 55 and under on the basis of their first name, the name of others in their household, and their length of residency. The final sample consisted of 60,814 women.

7.2.3 Stages of data collection

The NWHS data collection procedure was divided into two separate stages. Stage 1 consisted of the initial screening questionnaire and was sent in late 2001 to the sample of 60,814 women identified during sampling as likely to be aged 55 and under. A copy of this questionnaire is included in Appendix 2.1. The Stage 1 questionnaire was designed to assess eligibility for the full study, and also asked for brief details of all pregnancies experienced by the participant as well as several questions on any infertility and treatment for infertility. The form contained 'opt-out' boxes for the main exclusion criteria: under 18, over 55, never been pregnant and never attempted to get pregnant. Women were also able to specify that they did not wish to take part. A flowchart of the progress of women through the study is presented in Figure 7.1. Of the 60,814 questionnaires sent, 26,050 women replied. Approximately half of these women (13,015) did not wish to participate (n=2,738) or were ineligible (aged >55 yrs or otherwise ineligible n=5,664, aged <=55 yrs never/not yet tried to get pregnant n=4,713). Thus, 13,035 usable questionnaires were returned for Stage 1, of whom 11,424 women agreed to be re-contacted for Stage 2.

For Stage 2, 10,828 questionnaires were sent out (11,424 less 212 women who only ever had a termination of pregnancy for non-medical reasons, and 384 women who only returned their Stage 1 questionnaire once the Stage 2 mailing had been completed). Questionnaires were returned by 7,882 women, including 180 women who no longer wished to participate. This resulted in 7,702 usable questionnaires returned for Stage 2. A copy of the Stage 2 questionnaire is included in Appendix 2.2.

The Stage 2 questionnaire was considerably more detailed than the initial Stage 1 questionnaire, collecting information on much wider range of variables including types of fertility treatment and TTP. Therefore, Stage 2 allows for a more detailed

investigation of the epidemiology of infertility compared to Stage 1 data. A comparison of the characteristics of the women responding to both Stage 1 and Stage 2 is presented in the next chapter. For the further analyses using multivariate methods to look at the association between infertility and past reproductive outcomes, the Stage 2 sample was used, but further exclusion criteria applied. These criteria varied according to the definition of infertility used and are discussed in more detail in the next chapter.

7.2.4 Data collection tools

Stage 1 questionnaire

Data collected in this initial questionnaire was limited to questions about any self-reported infertility, any fertility treatment the woman or her partner had received, the timing of first consultation about infertility (if the woman had sought help), and the source of any fertility treatment received. Brief details were collected about each of the pregnancies experienced by the woman: the date pregnancy ended, multiplicity, pregnancy outcome, and whether the pregnancy resulted from fertility treatment.

Stage 2 questionnaire

The first part of the Stage 2 questionnaire collected information on the woman's date of birth, height, shoe size, educational qualifications and smoking history.

The second section of the questionnaire contained questions on infertility. Women were asked whether they had ever had problems trying to get pregnant, with the exact wording as follows: "Have you ever had any problems trying to get pregnant? (i.e. you tried for a baby and either didn't succeed in getting pregnant or took a long time to get pregnant)". If women answered "yes" to this question, they were then asked to indicate the date these problems first occurred, whether they had ever consulted a doctor because of difficulties getting pregnant, and whether they had ever received fertility treatment (and the date of their first consultation). Women were asked to report any fertility investigations that they or their male partner had undergone, along with any resulting diagnoses. Lastly, women were asked whether they or their male partner had ever received fertility treatment, and if so, what type of treatment and where it was received.

Next, the questionnaire comprised of a series of detailed questions about each pregnancy experienced by the respondent. Women were asked to provide the date of the pregnancy and her age and partner's age, the length and outcome of the pregnancy, and information on the baby if known (sex/multiple birth/weight). Women were also asked whether the pregnancy was planned, and if so, they were asked to indicate the time it took them to get pregnant (TTP) in grouped intervals (0-3 months, 3-6 months, 6-12 months, or over 12 months). Information was also collected on whether the pregnancy resulted from fertility treatment, any abnormalities with the pregnancy or baby, and any health problems suffered during the pregnancy.

In addition to the information described above, a number of other sections collected information on other reproductive and related experiences to be used in separate analyses of NHWS data. The most significant of these collected information specific to the woman's last pregnancy. These data was used in a case control analysis of risk factors for first trimester miscarriage.[109] To date, other published analyses using NWHS data have looked at whether gravidity influences smoking behaviour in pregnancy,[357] and qualitative experiences of miscarriage. [358]

7.2.5 Sample size and study power

The principle sample size calculation for the NWHS analyses was conducted according to the analysis looking at prior adverse reproductive events and the risk of secondary infertility. The exposure was taken as history of miscarriage (being the most common adverse outcome in pregnancy) and the self-reported definition of infertility was used.

Sample size calculations were done initially by hand using the formula for case-control studies provided by Kirkwood,[359] and were confirmed using the *statcalc* function in Epi Info (Epi Info version 6, Centers for Disease Control, Atlanta, GA USA).

The prevalence of prior miscarriage among women without infertility (controls) was estimated as 12%, in line with the prevalence found among all pregnancies in early descriptive analyses of NWHS data.[356] A series of calculations based on 80% power and a 5% significance level are presented in Table 7.1.

An odds ratio of 1.80 was chosen as plausible and suitable for the size of the study. According to the calculations performed, this would require a total minimum sample size of n=1112, equivalent to 278 cases (those with self-reported infertility) and 834 controls (those without self-reported infertility). In order to account for possible confounding, this number was increased by 50% (417 cases and 1251 controls). It has been suggested that a sample size should be increase fourfold in order to ensure power to detect effect modification.[339] However, this was considered to be impossible given the overall size of the NWHS sample.

7.2.6 Ethics

NWHS received ethical approval from the Multiple Regional Ethics Committee (MREC/01/4/009, 2001) and the LSHTM ethics committee (2001).

7.3 DATA PREPARATION

7.3.1 Data coding, checking and cleaning

The NWHS questionnaires were pre-coded for all but free text responses, and data entry was carried out by an external specialist company. The NWHS data had been subject to thorough data cleaning and checking before being made available. In addition to this, further checks were performed to look at improbable and extreme values, and to check consistency between variables.

7.3.2 Data manipulation

Infertility

As one of the aims of this thesis was to explore different definitions of infertility, the potential for multiple indicators of infertility in the NWHS data was exploited. The first and perhaps most straightforward indicator of infertility was a positive response to the question "Have you ever had any problems trying to get pregnant?". For this definition, the denominator was taken as all those with a valid response (Yes/No). This measure is referred to as 'self-reported infertility' throughout this thesis. If women responded positively to this question they were then asked about their contact with health professionals. Thus, the second indicator of infertility was derived from a "Yes" response to "Did you consult a doctor because you could not get pregnant?". Again, the

denominator here was the total number of women who had provided a valid response to these questions. This measure of infertility is henceforth referred to as 'help-seeking infertility'. The third and final indicator of infertility referred to the time to pregnancy (TTP) reported by women for each pregnancy. In existing literature, one of the most established definitions of infertility is an inability to conceive for 12 months or more. For this reason, women were defined as 'infertile' according to this definition if they reported at least one TTP of 12 months or more at some point during their reproductive life. This definition was clearly limited to those women who had been pregnant at least once, and the denominator was further limited to those women who had reported at least one TTP (i.e. those for whom all their pregnancies were described as 'unplanned' were not included). For ease of description, this definition of infertility is referred to as 'infertility TTP >12 months' or 'TTP-based infertility' in this thesis.

An early investigation of the data revealed that some women had included adverse outcomes such as miscarriage in the calculation of TTP. In these cases, the TTP was reset to reflect the actual interval between the end of the last pregnancy and the conception of the current pregnancy.

Timing of infertility

For each of the infertility definitions, a variable indicating the date of the first infertility event was calculated where possible. This was necessary in order to establish the order of reproductive events in a woman's life. For the first definition (self-reported problems conceiving), women were asked to remember the time they first had problems getting pregnant, and to provide the date they first started to try to get pregnant during this episode. Where an exact date was not given, mid-points of the month or year provided were used. If this date was missing but women had reported the date of their first consultation for fertility problems, this date was used instead. For the second definition (ever consulted), the date provided by women as the first time they went to doctor was used. As before, mid-points were used where the date given was not exact. For the third definition of infertility (TTP >12 months), the date of conception of the pregnancy *first* involving a TTP of 12 months or more was used to represent first episode of infertility. These date variables were used in their raw form to generate other variables indicating the events before and after the first episode of infertility, and were also used to generate variables indicating the age of the women when infertility was first experienced.

Reproductive events

Outcomes of all completed pregnancies and other pregnancy attempts were essential variables in the analysis. All pregnancies ending below 16 weeks were coded as singleton, even if reported as a multiple pregnancy. This decision was taken as screening is not universal below this gestation and therefore multiplicity would be commonly unknown at this gestational age.

Pregnancy outcome

Each pregnancy was coded according to outcome: livebirth, stillbirth, miscarriage (spontaneous abortion), termination (induced abortion), or ectopic pregnancy. Missed abortions and blighted ova were included in the miscarriage category. A variable was created to indicate whether a woman had ever experienced each of these events, and if so the total number of events experienced. Some of the analyses in this thesis were based on pregnancies or pregnancy attempts, with multiple records per woman. In preparation for these analyses, each pregnancy or attempt was ordered chronologically and the cumulative (past) number and subsequent (future) number of each event by woman was calculated. All pregnancy outcomes were taken into account, even if a specific analysis plan resulted in exclusions of certain records.

Miscarriage was defined as fetal death before 24 completed weeks of pregnancy, and was further sub-divided into early (up to 14 weeks) and late miscarriages (14 to less than 24 weeks). Some women reported miscarriages when the relevant pregnancy had ended in fetal death beyond 24 weeks, these were re-coded as stillbirths in line with the current UK definition which classifies fetal death occurring at a gestational age of 24 weeks or beyond as a stillbirth.

Terminations were divided into those that were medically indicated (where there was a problem with the woman or her baby), and those carried out in the absence of a clinical indication (sometimes described as 'social' terminations in the literature).

There were several cases of discordant outcomes among multiple births, and this posed a problem as only one pregnancy outcome (livebirth, stillbirth, miscarriage, termination

or ectopic pregnancy) could be recorded for each pregnancy. As a general rule, where at least one adverse pregnancy outcome occurred, the pregnancy was flagged as ending in this way even if a live birth had also occurred. There were three sets of twins where one was liveborn and the other stillborn, and four sets of twins where one twin was liveborn and the other miscarried (>16 weeks and less than 24 weeks). These pregnancies were coded as ending in the adverse outcome. Two sets of twin pregnancies where one fetus was miscarried and the other fetus was coded as an ectopic pregnancy were coded as ectopic. One pregnancy reported as ending in both miscarriage and termination was coded as a termination.

Preterm birth and low birthweight

Preterm birth and low birthweight were defined using established cut-offs for singletons and adapted cut-offs for multiple births. Singleton births occurring at less than 37 completed weeks were defined as preterm, and singleton births with a birthweight of less than 2500 grams were defined as low birthweight. These established cut-offs were considered inappropriate for use with multiple births, as twins and higher order multiples are known to have a lower mean birthweight and tend to be born at earlier gestations than singletons. Therefore, new thresholds were calculated using the equivalent percentile distribution for birthweight and gestation among multiples. Thirty-seven weeks and 2500 grams represented the 7.5 percentile and 5.3 percentile of the distributions for singleton births, and the equivalent values for multiples was 32 weeks and 1500 grams respectively (rounded up to the nearest complete week/ 100 grams). Preterm births among multiples was therefore defined as a livebirth at a gestation of less than 32 weeks, and multiple births were flagged as low birthweight where at least one infant was liveborn at a birthweight below 1500 grams.

Age

Age at survey was defined as the age of the woman at the survey inception (01/11/01), and was categorised into six roughly equal groups (<30, 30-34, 35-39, 40-44, 45-49, ≥50). Age at first fertility consultation was calculated using the reported date of first fertility consultation, and grouped in the following bands: <30, 30-34, 35-39, and ≥40.

Age of the woman was categorised into six groups (<20, 20-24, 25-29, 30-34, 35-39 and ≥40) for descriptive analyses, and collapsed into four groups (<24, 25-29, 30-34, ≥35) for multivariate analyses. For the descriptive work on the epidemiology of infertility, age was taken at pregnancy end. For analyses looking at the association between past reproductive outcomes and infertility, age was taken at the point at which the woman was estimated to begin trying to get pregnant (the start of the pregnancy attempt). The date at the start of the pregnancy attempt was calculated as age at the date they first reported trying to get pregnant for those women who self-reported problems trying to get pregnant during the index pregnancy or pregnancy attempt. For planned pregnancies where a TTP was reported, age at pregnancy attempt was taken at the mid-point of the TTP interval (e.g. for a woman reporting a TTP of 3-6 months, age at 4.5 months before conception) or 18 months before conception for women reporting a TTP of 12 months or more. Where the pregnancy was unplanned or TTP was missing, age at pregnancy attempt was taken at conception of the pregnancy.

Year of event

Pregnancies and pregnancy attempts were grouped into six categories according to their year of occurrence - <1980, 1980-84, 1985-89, 1990-94, 1995-99, 2000-02. For the focus on the epidemiology of infertility, the year of first pregnancy and the year the current pregnancy occurred were calculated using the date of pregnancy end. For the analyses looking at past outcomes and infertility, age of the woman was taken at the point which the pregnancy attempt was estimated to have begun.

7.4 ANALYSIS PLAN

All statistical analyses were conducted using STATA 10 (Stata Corporation, College Station, TX USA). Unless specified otherwise, a probability of 0.05 was used as the limit of statistical significance for all tests. All reported p-values were two-sided.

7.4.1 Aim 1: descriptive epidemiology of infertility

Specific objectives

To measure the prevalence of infertility and use of infertility treatment in the UK:

- To describe the characteristics of women in the NWHS cohort
- To report prevalence estimates of infertility

- To examine the similarities and differences in prevalence when using different measures of infertility
- To describe trends in infertility by age
- To describe the clinical diagnoses associated with infertility
- To investigate the characteristics of women who seek and receive medical help for infertility.
- To measure the proportion of women who have treatment for infertility and who subsequently have a birth.
- To compare the observed and expected number of reproductive events ever experienced according to infertility status.

Sample

The work carried out looking at the descriptive epidemiology of infertility made use of both Stage 1 and Stage 2 data. The analysis of Stage 1 data was restricted to the 6584 women who were aged 40-55 years at the time of survey. The lower age limit was chosen in order to examine complete, rather than partial, reproductive experience. Further details of this analysis are reported in the published article,[73] a copy of which is enclosed in Appendix 3. The work on Stage 1 was limited to basic indicators of infertility prevalence (unresolved infertility, the proportion consulting a doctor about fertility problems, the number receiving fertility treatment, and the proportion reporting at least one pregnancy conceived by infertility treatment), reflecting the limited information collected in the Stage 1 questionnaire.

For the broader look at the epidemiology of infertility using Stage 2 data, all 7702 Stage 2 responders were included. For most descriptive analyses conducted for this work, the unit of analysis was the woman.

Analysis

The focus here was on descriptive results, using summary statistics presented in cross tabulations and visual displays such as histograms and pie charts. The vast majority of results were presented by age at survey in order to differentiate those women likely to have completed their fertility. Prevalence estimates were presented where appropriate, with confidence intervals calculated using the Wald binomial method. Means and standard deviations were presented where the distribution was approximately normal,

for other variables with a non-normal distribution and/or extreme values the median was presented along with the range of values. A simple form of indirect standardisation was used to contrast the observed number with the expected number of reproductive events ever experienced according to infertility status. Using this method, the number of expected events among infertile groups was calculated by applying the age-specific observed rate for fertile women to each group of women who had experienced fertility problems. The result was a standardised event ratio (SER) for each pregnancy outcome. 95% confidence intervals were calculated. Formal statistical tests were not considered essential, although test for trends were calculated for some associations.

7.4.2 Aim 2: investigation of the effect of prior adverse reproductive outcomes on secondary infertility

Specific objectives

To explore the hypothesis that one or more prior adverse reproductive events has an impact on secondary infertility in women:

- To explore the timing of secondary infertility in terms of ever and prior reproductive events.
- To determine whether prior adverse reproductive events are associated with the risk of secondary infertility.

The analyses reported in this section used infertility as the starting point and looked retrospectively at reproductive history. By necessity, this involved a focus on secondary infertility – infertility where at least one previous pregnancy had been reported. More specifically, the association between past adverse pregnancy outcomes and secondary infertility was investigated, adverse pregnancy events being defined as pregnancies where any of the following events occurred: fetal death (miscarriage or stillbirth), termination, ectopic pregnancy, preterm birth or the birth of an infant with low birthweight.

The association between prior adverse outcomes and secondary infertility was explored using two different definitions of infertility. This resulted in two similar, but not identical, analyses being carried out.

The first approach was based on self-reported infertility, and necessitated an analysis based on a pregnancy *attempt* (successful or unsuccessful). The unit of analysis was a woman. The second approach looked at infertility as defined as a TTP of 12 months or more, and the unit of analysis was a pregnancy. Each woman could contribute multiple records to the analyses reported here, one record per pregnancy attempt.

Sample

This analysis used data taken from Stage 2 of NWHS. Due to the fact that this analysis looked at the association between past reproductive outcomes and infertility, only secondary infertility was considered. All first pregnancies or pregnancy attempts were excluded from the analyses. Truncation bias was also a consideration, with it likely that taking all pregnancies and pregnancy attempts up to the point of survey (01/11/01) would result in selection bias due to over-representation of 'quick conceivers'. Therefore, all pregnancy attempts estimated to begin on or after 01/11/99 (two years before the survey date) were excluded from these analyses.

The first approach using self-reported infertility was further limited to women who had specified whether or not they had ever had problems getting pregnant. In addition, only those women self-reporting problems who had also given the timing of this infertility could be included due to the need to be able to place the infertility event in chronological order. Lastly, as women were only asked in the NWHS questionnaire to report only the time they first experienced problems trying to conceive, this was a single-outcome analysis and pregnancy attempts occurring after their first episode of self-reported infertility were excluded. A flowchart displaying the number of women excluded from the analysis at each stage is presented in Chapter 9.

In the analysis using TTP of 12 months or more as the definition of infertility (TTP-based infertility), the analysis was limited to pregnancies that were reported as planned and where a (grouped categorical) TTP was reported. Women were able to report a TTP for each of their pregnancies (if more than one) so it was possible for women to contribute more than one event in this analysis. Again, the numbers of pregnancies fulfilling these criteria are described in Chapter 9.

Potential confounders and effect modifiers

Several confounders were considered key in the analyses. The age of the woman at the index pregnancy or pregnancy attempt (or her year of birth), and the year in which the pregnancy or pregnancy attempt commenced were both considered strong *a priori* confounders and were included in all adjusted analyses for completeness. The number of previous pregnancies or pregnancy attempts (equivalent to gravidity in the pregnancy-based analysis) was also considered a potential confounder, although the possibility that this factor would be heavily correlated with past outcomes meant that caution was exercised in adjusting for this variable. As reported in Chapter 3, there is strong evidence to support the link between ectopic pregnancy and reduced fertility, and for this reason prior ectopic pregnancy was also considered a possible confounder in the analysis of other adverse outcomes and infertility. This was the only situation in which another prior outcome was taken into account when looking at a specific prior outcome.

Whether or not a pregnancy resulted from the use of fertility treatment was considered of relevance to the analyses looking at TTP based infertility. However, this factor was thought to have a complex relation to the exposure and outcome under study, and it could not be considered a confounder in the classical sense. A long TTP would almost certainly precede the use of treatment, and adjusting for the use of fertility treatment would therefore be inappropriate as it could be considered to be on the causal pathway. While the distribution of pregnancies associated with fertility treatment was examined in descriptive analyses, this variable was not included as a potential confounder in multivariate analyses. An additional problem was that the use of fertility treatment may lead to inaccurate recall of the TTP, as women may report only the time to conception since the commencement of treatment (with a long period of time trying to conceive experienced before treatment started). For this reason, the final models for TTP based infertility were applied to a sample excluding all those pregnancies resulting from fertility treatment in an effort to assess the sensitivity of the association to treatment effects.

Statistical plans

To begin, a descriptive look at the distribution of key variables by pregnancy or pregnancy attempt order was carried out. This included the characteristics of the first

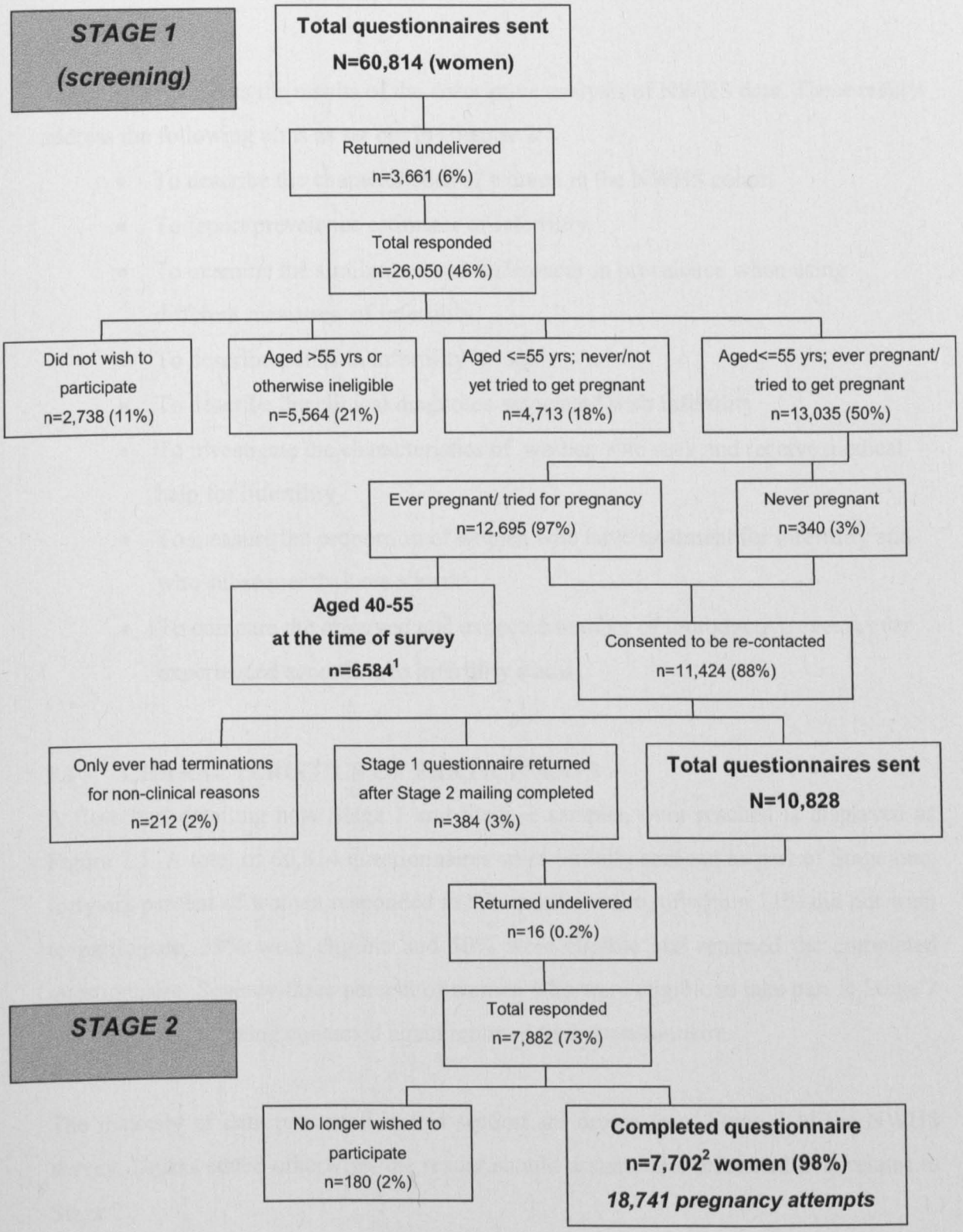
pregnancies or pregnancy attempts that were subsequently excluded from the analyses. Characteristics of each pregnancy or pregnancy attempt were considered here, along with the timing and age of the woman. For the analysis focussing on TTP, TTP groupings were also tabulated against the outcome of each pregnancy and by likely confounders or effect modifiers of the main associations of interest. Likely confounders were tabulated against the odds of self-reported infertility. The main analyses calculated the odds of infertility (however defined) according to a past history of each of the adverse pregnancy events. These were calculated according to the adverse event occurring in any past pregnancy, and also according to whether the adverse event occurred in the pregnancy directly preceding the infertility (last pregnancy). Logistic regression was used to calculate crude and adjusted odds ratios, the latter adjusted by *a priori* confounders and other factors thought to be confounding according to results obtained earlier. Since women could have more than one record (pregnancy or pregnancy attempt) in the analysis, a robust method based on the "sandwich estimate"[360] was used to compute standard errors, with Wald tests to test statistical significance of parameters.[361] This addressed possible clustering in the dataset. Basic stratified analyses were conducted to look for the possibility of effect modification, but this line of investigation was not pursued due to concerns about study power not being sufficient for a thorough investigation.

Table 7.1: Minimum sample size assuming 10% prevalence (ratio of 3:1 controls to cases)

Power	Alpha[1]	Odds ratio	Controls n	Cases n
0.80	0.05	1.40	2751	917
0.80	0.05	1.50	1854	618
0.80	0.05	1.60	1353	451
0.80	0.05	1.70	1041	347
0.80	0.05	1.80	834	278
0.80	0.05	1.90	690	230
0.80	0.05	2.00	582	194

[1]Two-sided test

Figure 7.1: Flowchart of Stage 1 and Stage 2 samples



[1]Sample used in analysis of Stage 1 data
[2]Sample used in analysis of Stage 2 data

Chapter 8: National Women's Health Study - Results 1

This chapter presents the results of the descriptive analysis of NWHS data. These results address the following aims as set out in Chapter 2:

- To describe the characteristics of women in the NWHS cohort
- To report prevalence estimates of infertility
- To examine the similarities and differences in prevalence when using different measures of infertility
- To describe trends in infertility by age
- To describe the clinical diagnoses associated with infertility
- To investigate the characteristics of women who seek and receive medical help for infertility
- To measure the proportion of women who have treatment for infertility and who subsequently have a birth
- To compare the observed and expected number of reproductive events ever experienced according to infertility status.

8.1 CHARACTERISTICS OF PARTICIPANTS

A flowchart detailing how Stage 1 and Stage 2 samples were reached is displayed as Figure 7.1. A total of 60,814 questionnaires were initially sent out as part of Stage one, forty-six percent of women responded to this questionnaire, of whom 11% did not wish to participate, 39% were eligible and 50% were eligible and returned the completed questionnaire. Seventy-three percent of women who were eligible to take part in Stage 2 and consented to being contacted again returned their questionnaire.

The majority of data presented in this section are drawn from Stage 2 of the NWHS survey. Unless stated otherwise, the reader should assume that presented data relates to Stage 2.

8.1.1 Basic characteristics

Table 8.1 describes the basic characteristics of the women in both Stage 1 and Stage 2 of NWHS, and Table 8.2 describes the pregnancies reported by them. The age of women at the NWHS survey (Stage 1 and 2) is slightly skewed by age, with one third of responders over the age of 45 and only ten percent under the age of 30. The number of pregnancies reported by each woman ranged between 0 and 18, with a median of two pregnancies per women. The year of first pregnancy reported by NWHS women ranged from 1963 to 2002. A significant minority of women reported problems with fertility: 16% had consulted a doctor because of problems getting pregnancy, eight percent had ever had fertility treatment and four percent had conceived at least one pregnancy as a result of fertility treatment. Of the pregnancies reported by NWHS women, the vast majority ended in a livebirth (80%). Thirteen percent ended in miscarriage, and four percent in a termination. A small number of stillbirths, ectopic and molar pregnancies were reported. A comparison of the characteristics of those that responded to Stage 1 and Stage 2 shows that the two samples are very similar.

8.2 PREVALENCE OF INFERTILITY AND TREATMENT-SEEKING BEHAVIOUR

8.2.1 Overall trends and trend by age

Unresolved infertility

For Stage 1 data, the prevalence of unresolved infertility is presented in Table I of the published paper, a copy of which is contained in Appendix 3. The prevalence estimates are stratified by grouped year of birth. One in 40 (2.4%) women reported never being pregnant despite trying (primary unresolved infertility), and one in twenty-five (4.3%) had never achieved a live birth. There was no evidence to support a birth cohort effect in either of these measures.

The prevalence of unresolved infertility reported in the smaller Stage 2 sample was almost identical: 2.5% and 5.1% for the two measures respectively (Table 8.3). Younger age groups reported a higher prevalence of both measures of unresolved infertility, although a test for linear trend was only strongly significant for the 'never livebirth' measure (p values for trend <0.001 for 'never livebirth' and 0.08 for 'never pregnant').

Among women aged 40-55 at survey, there was a slight trend of decreasing prevalence of both types of unresolved infertility with increasing age, although these trends were not statistically significant (p values for trend 0.83 and 0.37, respectively).

Self-reported problems conceiving

This measure of infertility was only available from Stage 2 data. Overall, one in five women reported having problems getting pregnant at some point in their reproductive career (Table 8.4). This figure peaked in the 35-39 age group, with younger and older age groups reporting a slightly reduced risk of self-reported infertility. Looking at women aged 40-55, those aged 40-44 reported the highest prevalence and women aged over 50 reported the lowest prevalence (p value for trend 0.04).

Consultations and treatment for fertility problems

The proportion of women who reported having ever consulted a doctor about problems conceiving and those who had received fertility treatment was reported in both Stage 1 and Stage 2. The data for Stage 1 is presented in Figure 1 and Table II of the published paper. Sixteen percent of Stage 1 respondents reported that at some point they had consulted a doctor about problems conceiving and eight percent had received fertility treatment. There were significant trends with age, with more recently born women more likely to both consult a doctor and receive fertility treatment.

Similar patterns were observed in the Stage 2 data, presented in Table 8.5. As in Stage 1, sixteen percent of women reported seeking medical help because of problems conceiving, and half of these (8%) went on to receive fertility treatment. Both of these figures were slightly lower among both the youngest and oldest age groups, with the highest prevalence observed for women aged 35-39 at survey. Again, both of these factors showed a significant decreasing trend with increasing age among women aged 40-55 (p values for trend 0.03 and 0.005).

Age at first fertility consultation for all Stage 1 respondents who consulted about fertility problems is presented in Table II of the enclosed paper. These data show that later born women tend to first consult at a slightly older age than earlier born birth cohorts.

The equivalent data for Stage 2 respondents is presented in Table 8.6. Concentrating on the group of women most likely to have completed their fertility (40+), we can see that more recent birth cohorts tended to first consult at a slighter later average age. For example, the mean age at consultation was 28.2 years for women ≥50, and 30.3 years for women aged 40-44.

Time to pregnancy measure

Of those women reporting at least one TTP, 16% had experienced at least one TTP of 12 months or more (Table 8.7). This figure was slightly lower among women below the age of 35. When women aged 40-55 were stratified into five-year age groups, there was no evidence that the proportion of women who reported ever experiencing conception delay of 12 months or more differed by age group (p value for trend 0.92).

Time to pregnancy by maternal age at birth for all reported planned pregnancies is displayed in Figure 8.1. This shows a trend for increased maternal age to be associated with longer TTP. A TTP of 12 months or more was reported for 4.1% of pregnancies occurring to women under the age of 20, rising to 24.1% of pregnancies in women aged 40 or over.

Overlap between different definitions of infertility

One of the unique features of the NWHS is that information was collected on multiple indicators of infertility. Whilst only a small minority of women reported unresolved infertility, the other measures of infertility described above resulted in a larger number of women being classified as having experienced infertility. A comparison of these different definitions is displayed in Figure 8.2. This comparison was restricted to women who had reported at least one TTP in order to ensure that an equivalent denominator was used across all definitions. Overall, the self-reported measure of infertility was the most commonly reported measure of infertility at 18%. Indicators of infertility based on ever consulting a doctor and ever experiencing a TTP of 12mths or more were slightly lower, at 15-16% of women. Around seven percent of women had ever received fertility treatment. There were distinctive age-related trends in the proportion of women classified as infertile according to all three definitions. The 30-34

age group had the lowest number of women classified as infertile, with the 15-29 age group showing slightly higher levels. The age group reporting the highest prevalence of infertility (according to all definitions) was 35-39, with levels decreasing in each subsequent age group.

Figure 8.3 shows a proportional Venn diagram representing all the women who could be described as experiencing infertility using at least one of the three definitions (self-reported infertility, ever consulted a doctor because of problems conceiving, and ever experiencing at TTP of 12 months or more). As opposed to the previous figure, the data presented here also includes women who reported fertility problems but did not conceive. It is clear that there is a significant overlap between the definitions, with nearly half (47%) of women reporting infertility according to all three definitions of infertility. Eighteen percent of women reported two measures out of three, but did not experience a long TTP (this may be because they never conceived a pregnancy). Fifteen percent reported at least one TTP but no other indictors of infertility. One in 10 reported problems conceiving and at least one TTP, but did not ever consult a doctor. Approximately one quarter of women were classified as infertile according to one definition only.

8.3 INFERTILITY INVESTIGATIONS AND TREATMENT

8.3.1 Investigations and diagnoses

Just over one thousand women (n=1036) reported that they and/or their male partner had at some point had been clinically investigated for infertility problems (Figure 8.4). In the vast majority of cases (83%) both partners had been investigated. The second pie chart in this diagram displays the outcome of these investigations. In 35% of cases, only a female factor for infertility was diagnosed. Thirteen percent of investigations revealed a male factor cause only, and 16% revealed both female and male factor. A high proportion – 19% - of investigations revealed no obvious cause of infertility ('unexplained infertility').

Table 8.8 lists the diagnoses resulting from infertility investigations in women. The denominator here is the 1005 women who reported that they had been investigated for infertility problems, excluding the 31 women who reported that only their male partner

had been investigated. Among all women reporting investigation, in 30% of women no problem was found, and an additional four percent of women reported results were still pending or not known. Of those reporting at least one diagnosis, the most common diagnosis was ovulatory problems, present in 42% of women. One in five women reported tubal factor infertility, and 17% had been diagnosed with endometriosis. One third of women reported that another diagnosis had been made, these included polycystic ovarian syndrome (PCOS), premature ovarian failure (early menopause), hyperprolactinaemia, and uterine fibroids.

8.3.2 Treatment received

Six hundred and eighteen (eight percent of the total sample) women reported that they and/or their husband or partner had received fertility treatment to help them get pregnant. The details of what fertility treatment was received (where these details were reported, n=598) is presented in Table 8.9. Just over half of women reported receiving drugs only treatment, and overall one quarter had received IVF/ICSI (with or without other ART). Fourteen percent had received other ART only, and seven percent had received other (non-ART) treatment. Women reported the type of treatment received where this was not ART using free text boxes. Examples of commonly received treatments listed here included laparoscopy, vasectomy reversal and tubal surgery. The highest prevalence of IVF/ICSI use was reported by middle age groups (consistently ≥25%). The prevalence of the use of other treatment increased with age at survey.

8.3.3 Pregnancies conceived through as a result of fertility treatment

The proportion of Stage 1 respondents aged 40-55 years who conceived at least one pregnancy as a result of fertility treatment is present in Table III of the published paper. Approximately one in 25 women (4.2%) who had been pregnant reported at least one pregnancy conceived in this way. There was a strong evidence of a trend with birth cohort, with more recently born birth cohorts reporting a higher proportion of pregnancies resulting from fertility treatment.

The proportion of women who reported at least one pregnancy conceived as a result of fertility treatment was almost identical in the smaller Stage 2 sample – 4.4% (Table 8.10). Three quarters of these women reported only one pregnancy conceived through in

this way. Twenty-one percent reported two fertility treatment pregnancies, and a small number (4%) had three or more pregnancies conceived in this manner. Unsurprisingly, the youngest age group (<30) reported the smallest proportion of fertility treatment conceived pregnancies. Concentrating on the 40+ cohorts, we can see a clear trend by birth cohort with women ≥50 years reporting a smaller proportion of pregnancies resulting from fertility treatment (3.8%) compared to women aged 40-44 years (6.3%).

8.4 REPRODUCTIVE OUTCOMES BY INFERTILITY STATUS

8.4.1 Pregnancy outcomes ever experienced by infertility status

As a precursor to the analyses looking at the effect of previous reproductive outcomes on infertility, standardised event ratios (SERs) were calculated to look at the risk of ever experiencing various reproductive outcomes according to infertility status. These results, along with the expected and observed figures used to calculate the SERs, are presented in Table 8.11, Table 8.12 and Table 8.13. Each table uses a different definition of infertility, and the data reflect outcomes reported at all ages, both preceding and subsequent to any reported infertility. Women who had never had a pregnancy were included in these analyses, although women who had not yet completed their first pregnancy were excluded.

Table 8.11 uses the self-reported definition of infertility. The crude SERs reported in this table show that compared to women who did not report problems trying to get pregnant, those women who self-reported problems were 19% less likely than expected to ever experience a livebirth (SER 0.81, 95% CI 0.77-0.86). Women with self-reported infertility were 65% more likely to report ever having a miscarriage (SER 1.65, 95% CI 1.51-1.81), and 1.2 and 3.9 times more likely to report a history of termination and ectopic pregnancy respectively (SER 1.21, 95% CI 1.00-1.42; SER 3.90, 95% CI 2.77-5.06). The number of women with self-reported infertility who had ever experienced a stillbirth was not statistically significantly different from expected.

In Table 8.12, women were stratified according to whether they had ever consulted a doctor because of problems trying to conceive ('help-seeking infertility'). Women falling into this category were 8% less likely to report a livebirth when compared to

those women who had never consulted a doctor (SER 0.92, 95% CI 0.86-0.98). They were also 1.5 times more likely to report ever having had a miscarriage and 3.6 more likely to report an ectopic pregnancy (SER 1.55, 95% CI 1.40-1.70; SER 3.59, 95% CI 2.46-5.72). The number of women experiencing a stillbirth or termination did not differ significantly according to whether a woman had ever consulted a doctor because of problems conceiving.

Finally, Table 8.13 presents similar calculations using infertility defined as at least one TTP of 12 months or more. Using this definition, compared to women who had never experienced conception delay, women with infertility were 1.5 times more likely to report ever having had a miscarriage (SER 1.57, 95% CI 1.40-1.73) and 3.5 times more likely to report ever having a ectopic pregnancy (SER 3.55, 95% CI 2.37-4.72). There were no significant differences in the number of women reporting ever having a livebirth, stillbirth or termination according to their infertility status, when this was defined as at least one TTP of 12 months or more.

8.4.2 Pregnancies subsequent to fertility treatment

The proportion of women who received fertility treatment of any kind and then went on to subsequently conceive a pregnancy or deliver a liveborn infant at some point in the future is reported in Table 8.14. Overall, 92.6% of women receiving fertility treatment went on to conceive a pregnancy and 91.5% went on to experience a live birth. These outcomes followed treatment for infertility, but were not necessarily attributable to treatment. There was a marked trend by age at first consultation for fertility, with those consulting at an earlier age more likely to report a positive outcome. Nearly ninety-seven percent of those who were <24 at first consultation went on to conceive a pregnancy, compared to 86.7% who first consulted at 40 or over. This gap widened further when the outcome was a livebirth: 95.6% of those first consulted at <24 had a livebirth after treatment, compared to 80.0% of those aged 40 or over at their first consultation.

Table 8.1: Characteristics of women responding to Stages 1 and 2 of NWHS

	STAGE 1		STAGE 2	
	n	(%)	n	(%)
TOTAL NUMBER OF WOMEN	13035		7702	
Age at survey				
<30	1433	(11.1)	709	(9.2)
30-34	2189	(17.0)	1325	(17.2)
35-39	2677	(20.8)	1665	(21.6)
40-44	2443	(19.0)	1476	(19.2)
45-49	2011	(15.6)	1193	(15.5)
≥50	2130	(16.5)	1332	(17.3)
Missing	152		2	
Mean age (SD)	*40.5 (8.4)*		*40.3 (8.3)*	
Total number of pregnancies reported per woman				
0	340	(2.6)	194	(2.5)
1	2607	(20.0)	1403	(18.2)
2	5077	(38.9)	3162	(41.1)
3	2962	(22.7)	1749	(22.7)
4	1573	(12.1)	818	(10.6)
5	285	(2.2)	229	(3.0)
≥6	191	(1.5)	147	(1.9)
Median (range)	*2 (0-18)*		*2 (0-18)*	
Year of first pregnancy[1]				
<1980	3201	(26.2)	1798	(23.9)
1980-84	1902	(15.6)	1131	(15.1)
1985-89	2091	(17.1)	1259	(16.8)
1990-94	2158	(17.7)	1356	(18.1)
1995-99	2079	(17.0)	1406	(18.7)
2000-02	788	(6.4)	558	(7.4)
Missing	476		0	
Conceived at least one pregnancy as a result of fertility treatment[1]				
Yes	524	(4.1)	327	(4.4)
No	12171	(95.9)	7181	(95.6)
Ever consulted a doctor because of problems getting pregnant				
Yes	2035	(15.6)	1256	(16.3)
No	11000	(84.4)	6446	(83.7)
Ever had fertility treatment to help get pregnant				
Yes	999	(7.7)	618	(8.0)
No	12036	(92.3)	7084	(92.0)
Age at first fertility consultation[2]				
<25				
25-29	927	(61.8)	710	(61.4)
30-34	378	(25.2)	297	(25.7)
35-39	152	(10.1)	115	(9.9)
≥40	43	(2.9)	35	(3.0)
Missing	535		99	
Mean age (SD)	*28.8 (5.2)*		*28.8 (5.2)*	

[1]Among women reporting at least one pregnancy
[2]Among women who reported ever consulting a doctor

Table 8.2: Characteristics of pregnancies reported in Stages 1 and 2 of NWHS

		STAGE 1 n	STAGE 1 %	STAGE 2 n	STAGE 2 %
TOTAL REPORTED PREGNANCIES		30660		18390	
Outcome of pregnancy					
Livebirth, surviving >7 days		24081	79.3%	14782	80.4%
Livebirth, early neonatal death		95	0.3%	56	0.3%
Stillbirth		188	0.6%	110	0.6%
Miscarriage		3511	11.6%	2325	12.6%
Ectopic		226	0.7%	102	0.6%
Termination for medical reasons		312	1.0%	89	0.5%
Termination for non-medical reasons		1424	4.7%	562	3.1%
Molar pregnancy		47	0.2%	26	0.1%
Ongoing (current) pregnancy		482	1.6%	338	1.8%
Missing		294		-	
Year of pregnancy end					
<1980		6093	20.5%	3486	19.0%
1980-84		4503	15.2%	2623	14.3%
1985-89		5028	16.9%	3000	16.3%
1990-94		5549	18.7%	3434	18.7%
1995-95		5807	19.6%	3864	21.0%
2000-02		2721	9.2%	1983	10.8%
Missing		959		-	
Pregnancy conceived as a result of fertility treatment					
No		29928	97.8%	17957	97.6%
Yes		685	2.2%	431	2.3%
Missing		47		2	
If yes,	Drugs only	352	65.4%	275	63.8%
	IVF, GIFT or ICSI	123	22.9%	108	25.1%
	AID, AIH or IUI	62	11.5%	47	10.9%
	Other	1	0.2%	1	0.2%
	Missing	147		0	

Table 8.3: Women reporting unresolved infertility (never pregnant or never experiencing livebirth), by age at survey (Stage 2)

Age of woman at survey	Never pregnant			Never livebirth		
	Total N	n	Prevalence % (95% CI)	Total N	n	Prevalence % (95% CI)
15-29	709	24	3.4 (2.0, 4.7)	670	78	11.6 (9.2, 14.1)
30-34	1325	41	3.1 (2.2, 4.0)	1293	86	6.6 (5.3, 8.0)
35-39	1665	36	2.2 (1.5, 2.9)	1659	79	4.8 (3.8, 5.8)
40-44	1476	35	2.4 (1.6, 3.1)	1474	57	3.9 (2.9, 4.8)
45-49	1193	27	2.3 (1.4, 3.1)	1193	45	3.7 (2.7, 4.8)
≥50	1332	30	2.2 (1.4, 3.0)	1332	43	3.2 (2.3, 4.2)
All women	7700[1]	193	2.5 (2.2, 2.9)	7621[1,2,3]	388	5.1 (4.6, 5.6)

[1]Excluding 2 women who did not report age at survey
[2]Excluding 73 women currently pregnant with their first child
[3]Excluding 6 women who had only ever had terminations for non-medical reasons and had never consulted a doctor about fertility problems

Table 8.4: Women reporting ever problems conceiving, by age at survey (Stage 2)

Age of woman at survey	Self-reported problems conceiving			
	N	n	%	(95% CI)
15-29	705	122	17.3	(14.5, 20.1)
30-34	1316	257	19.5	(17.4, 21.7)
35-39	1648	355	21.5	(19.5, 23.5)
40-44	1464	294	20.0	(18.0, 22.1)
45-49	1173	232	19.8	(17.5, 22.1)
≥50	1315	224	17.0	(15.0, 19.1)
All women	7621[1,2]	1484	19.5	(18.6, 20.4)

[1]Excluding 2 women who did not report age at survey
[2]Excluding 79 women who did not report whether or not they had ever had problems conceiving

Table 8.5: Women reporting ever consulting a doctor about problems conceiving and ever receiving fertility treatment, by age at survey (Stage 2)

Age of woman at survey	Total	Ever consulted a doctor about problems conceiving			Ever received fertility treatment		
	N	n	%	(95%CI)	n	%	(95%CI)
15-29	709	100	14.1	(11.5, 16.7)	42	5.9	(4.2, 7.7)
30-34	1325	204	15.4	(13.4, 17.3)	87	6.6	(5.2, 7.9)
35-39	1665	298	17.9	(16.0, 19.7)	158	9.5	(8.0, 10.9)
40-44	1476	258	17.5	(15.5, 19.4)	139	9.4	(7.9, 10.9)
45-49	1193	202	16.9	(14.8, 19.1)	103	8.6	(7.0, 10.3)
≥50	1332	193	14.5	(12.6, 16.4)	86	6.5	(5.1, 7.8)
All women	7700[1]	1255	16.3	(15.5, 17.1)	615	8.0	(7.4, 8.6)

[1]Excluding 2 women who did not report age at survey

Table 8.6: Age at first fertility consultation for all women who consulted about fertility problems, by age at survey (Stage 2)

Age of woman at first consultation	Age of woman at survey													
	<30 consulted		30-34 consulted		35-39 consulted		40-44 consulted		45-49 consulted		≥50 consulted		All women consulted	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Total No. women	**88**	**(100)**	**186**	**(100)**	**275**	**(100)**	**236**	**(100)**	**191**	**(100)**	**181**	**(100)**	**1157[1]**	**(100)**
<25	53	(60.2)	50	(26.9)	41	(14.9)	46	(19.5)	49	(25.6)	48	(26.5)	287	(24.8)
25-29	35	(39.8)	78	(41.9)	96	(34.9)	74	(31.4)	64	(33.5)	76	(42.0)	423	(36.6)
30 - 34			58	(31.2)	109	(39.6)	58	(24.6)	35	(18.3)	37	(20.4)	297	(25.7)
35 - 39					29	(10.5)	44	(18.6)	30	(15.7)	12	(6.6)	115	(9.9)
≥40							14	(5.9)	13	(6.8)	8	(4.4)	35	(3.0)
Mean (sd)	24	(2.8)	27.5	(3.8)	29.7	(4.3)	30.3	(5.8)	29.7	(6.0)	28.2	(5.2)	28.8	(5.2)

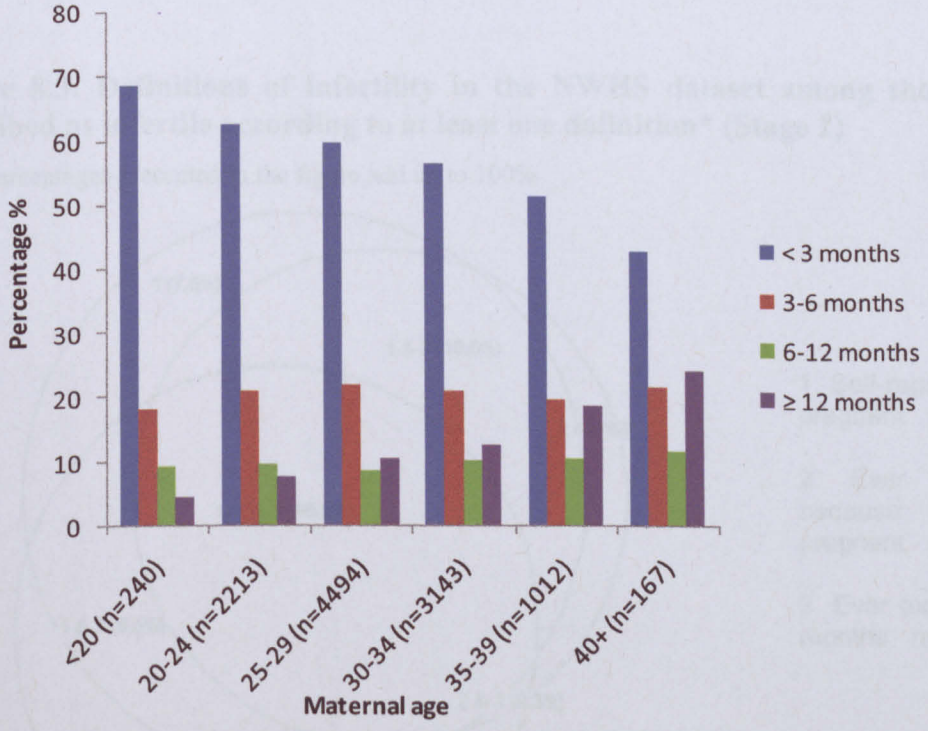
[1]Excluding 99 women who did not report age at consultation or for whom age at consultation could not be estimated

Table 8.7: Women reporting at least one TTP of 12 months or more by age at survey, among all women ever pregnant reporting at least one TTP (Stage 2)

Age of woman at survey	Ever had a TTP of 12 months or more			
	N	n	%	(95% CI)
15-29	430	59	13.7	(10.6, 17.0)
30-34	1076	129	12.0	(10.0, 13.9)
35-39	1422	244	17.2	(15.2, 19.1)
40-44	1246	213	17.1	(15.0, 19.2)
45-49	1016	173	17.0	(14.7, 19.3)
≥50	1104	187	17.0	(14.7, 19.1)
All women	6294[1]	1005	16.0	(15.1, 16.9)

[1]Excluding one woman who did not report age at survey

Figure 8.1: Time to pregnancy by maternal age at birth* (Stage 2)



* all pregnancies for which a TTP was available, n=11,269

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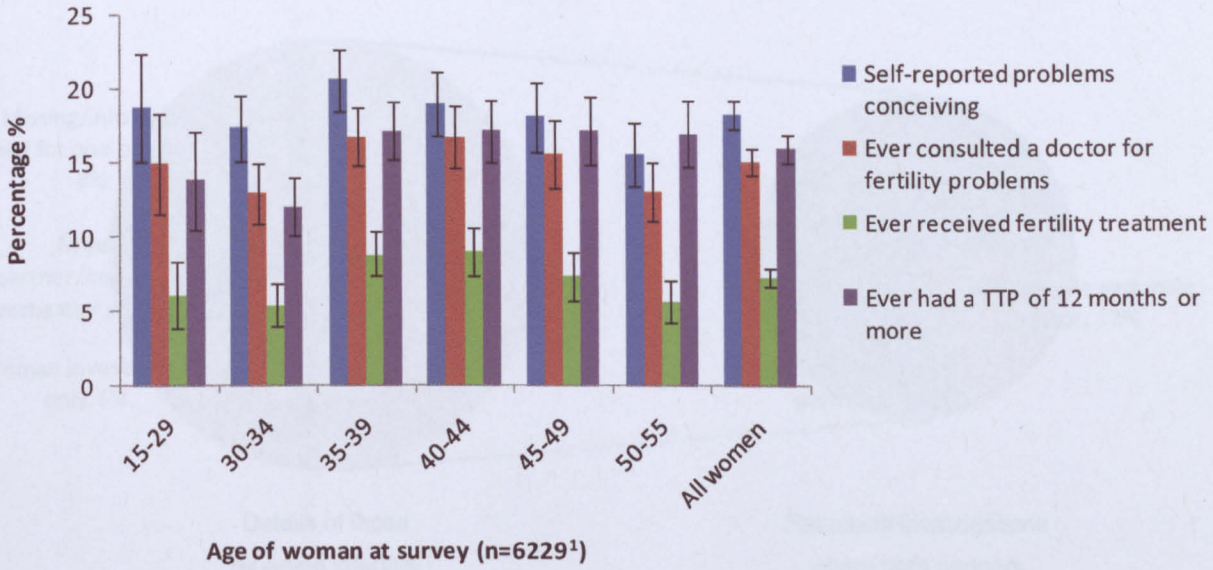
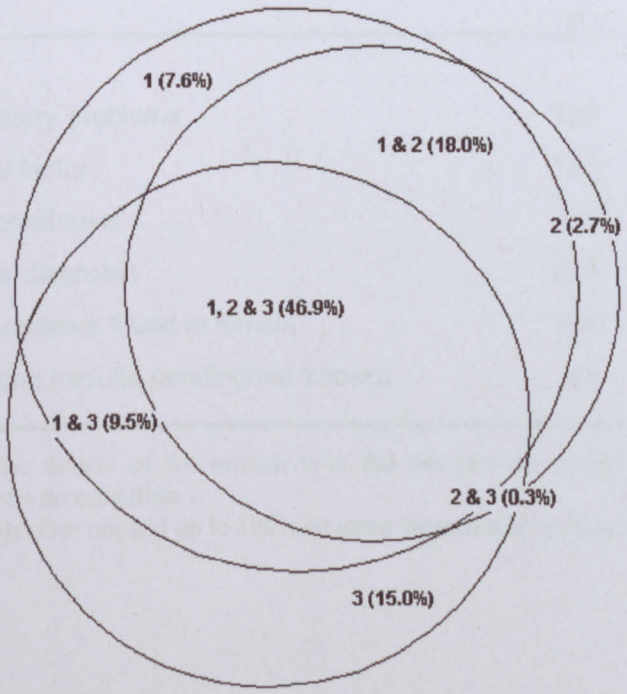
Figure 8.2: Percentage of women reporting infertility according to different definitions, by age at survey (Stage 2)



[1] Restricted to those women ever pregnant who had reported at least one TTP and those who had reported whether or not they had ever had problems trying to get pregnant

Figure 8.3: Definitions of infertility in the NWHS dataset among those women described as infertile according to at least one definition* (Stage 2)

N.B. Percentages presented in the figure add up to 100%



1. Self-reported problems getting pregnant n=1141

2. Ever consulted a doctor because of problems getting pregnant n=944

3. Ever experienced TTP of ≥12 months n=988

*(n=1391)

Figure 8.4: Results of infertility investigations (Stage 2)

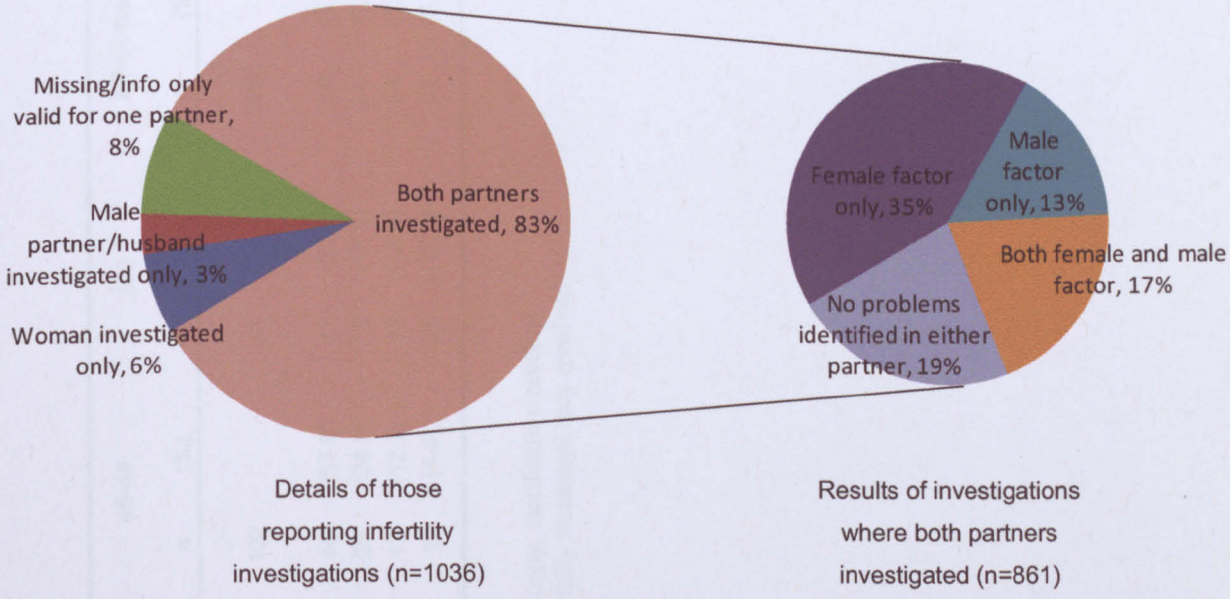


Table 8.8: Female factor diagnoses resulting from infertility investigations among all women reporting investigation (Stage 2)

Female factor diagnoses (N=1005[1])	n	All women (%)	Women with a diagnosis (%)
Ovulatory problems	283	(28.2)	(42.0)
Tubal factor	130	(12.9)	(19.3)
Endometriosis	114	(11.3)	(16.9)
Other diagnosis	225	(22.4)	(33.4)
No problems found in female	292	(29.1)	
Missing (results pending/not known)	39	(3.9)	

[1] Includes details of 81 women who did not provide details on whether their partner/husband had undergone investigation

N.b. table does not add up to 100% as some women had multiple diagnoses

Table 8.9: Type of fertility treatment received, by age at survey (Stage 2)

Type of fertility treatment received	<30		30-34		35-39		40-44		45-49		≥50		All women	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
All women receiving treatment	41		84		153		137		102		81		598[3]	
Drugs only	26	(63.4)	43	(51.2)	79	(51.6)	77	(56.2)	59	(57.8)	41	(50.6)	325	(5.4)
IVF/ICSI	8	(19.5)	21	(25.0)	45	(29.4)	35	(25.5)	25	(24.5)	13	(16.0)	147	(2.5)
Other ART[1]	6	(14.6)	14	(16.7)	23	(15.0)	16	(11.7)	13	(12.7)	12	(14.8)	84	(1.4)
Other treatment[2]	1	(2.4)	6	(7.1)	6	(3.9)	9	(6.6)	5	(4.9)	15	(18.5)	42	(0.7)

[1]Including AID, AIH, IUI, GIFT
[2]Including treatments for PCOS, treatments for endometriosis, treatments for thyroid disorders, laparoscopy, sterilisation reversal
[3]Excluding 1 woman who did not report age at survey and 17 women who did not report the type of fertility treatment they received

Table 8.10: Number of pregnancies conceived as a result of fertility treatment, by age at survey (Stage 2)

Number of pregnancies conceived through fertility treatment	Age of woman at survey												All women	
	<30		30-34		35-39		40-44		45-49		≥50			
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
All women	685		1284		1629		1441		1166		1302		7508[1]	
0	667	(97.4)	1239	(96.5)	1542	(94.7)	1357	(94.2)	1113	(95.5)	1263	(97.0)	7181	(95.7)
≥1	18	(2.6)	45	(3.5)	105	(6.4)	84	(5.8)	53	(4.5)	39	(3.0)	327	(4.4)
1	*13*	*(1.9)*	*35*	*(2.7)*	*71*	*(4.4)*	*57*	*(4.0)*	*40*	*(3.4)*	*27*	*(2.1)*	*244*[1]	*(3.2)*
2	*5*	*(0.7)*	*8*	*(0.6)*	*13*	*(0.8)*	*18*	*(1.2)*	*13*	*(1.1)*	*11*	*(0.8)*	*68*	*(0.9)*
3	*0*	*(0.0)*	*1*	*(0.1)*	*2*	*(0.1)*	*7*	*(0.5)*	*0*	*(0.0)*	*0*	*(0.0)*	*10*	*(0.1)*
4-5	*0*	*(0.0)*	*1*	*(0.1)*	*1*	*(0.1)*	*2*	*(0.1)*	*0*	*(0.0)*	*1*	*(0.1)*	*5*	*(0.1)*

[1]Excluding one woman who did not report age at survey

Table 8.11: Ratio of observed/expected events (ever experienced) according to infertility status (self-reported infertility) (Stage 2)

Age at survey			ever livebirth			ever stillbirth				ever miscarriage			ever termination			ever ectopic		
		N	O	E	(O/E)	O	E	(O/E)	N	O	E	(O/E)	O	E	(O/E)	O	E	(O/E)
15-29	ever self-reported infertility	113	72	104.9	0.69	0	1.2	0.00	115	34	22.7	1.50	9	10.5	0.86	5	0.8	6.22
	never self-reported infertility	556	516			6			572	113			52			4		
30-34	ever self-reported infertility	249	187	242.8	0.77	0	1.0	0.00	252	67	55.6	1.20	26	22.8	1.14	2	2.4	0.83
	never self-reported infertility	1037	1011			4			1051	232			95			10		
35-39	ever self-reported infertility	351	291	346.4	0.84	4	5.2	0.77	354	128	71.5	1.79	28	27.7	1.01	12	3.6	3.37
	never self-reported infertility	1291	1274			19			1292	261			101			13		
40-44	ever self-reported infertility	294	245	291.7	0.84	2	2.3	0.88	294	103	60.6	1.70	32	24.4	1.31	14	2.0	6.96
	never self-reported infertility	1169	1160			9			1169	241			97			8		
45-49	ever self-reported infertility	232	190	231.3	0.82	5	3.9	1.27	232	76	43.9	1.73	20	12.8	1.56	7	1.0	7.10
	never self-reported infertility	941	938			16			941	178			52			4		
50-54	ever self-reported infertility	224	184	223.4	0.82	10	6.2	1.62	224	73	38.2	1.91	14	9.6	1.45	5	1.8	2.71
	never self-reported infertility	1091	1088			30			1091	186			47			9		
Total	ever self-reported infertility	1463	1169	1439.4	0.81	21	20.2	1.04	1471	481	291.3	1.65	129	106.8	1.21	45	11.5	3.90
	never self-reported infertility	6085	5987			84			6116	1211			444			48		
	SER (95% CI)		**0.81**	**(0.77, 0.86)**		**1.04**	**(0.60, 1.48)**			**1.65**	**(1.51, 1.81)**		**1.21**	**(1.00, 1.42)**		**3.90**	**(2.77, 5.06)**	

Table 8.12: Ratio of observed/expected events (ever experienced) according to infertility status (ever consulted doctor because of problems trying to get pregnant) (Stage 2)

Age at survey			ever livebirth			ever stillbirth				ever miscarriage			ever termination			ever ectopic		
		N	O	E	(O/E)	O	E	(O/E)	N	O	E	(O/E)	O	E	(O/E)	O	E	(O/E)
15-29	ever consulted	94	58	86.7	0.67	0	1.0	0.00	95	24	19.6	1.22	7	8.6	0.81	6	0.5	12.55
	never consulted	579	534			6			596	123			54			3		
30-34	ever consulted	198	142	192.2	0.74	0	0.7	0.00	199	48	45.1	1.07	17	18.8	0.91	1	2.0	0.51
	never consulted	1097	1065			4			1113	252			105			11		
35-39	ever consulted	295	238	290.2	0.82	4	4.1	0.97	297	102	63.5	1.61	24	24.1	0.99	10	3.5	2.87
	never consulted	1364	1342			19			1366	292			111			16		
40-44	ever consulted	258	211	255.7	0.83	1	2.1	0.47	258	90	54.1	1.66	27	21.8	1.24	12	2.3	5.15
	never consulted	1217	1206			10			1217	255			103			11		
45-49	ever consulted	202	161	19.8	8.14	4	3.5	1.15	202	70	38.1	1.84	19	11.0	1.73	6	1.0	5.89
	never consulted	991	97			17			991	187			54			5		
50-54	ever consulted	193	154	192.3	0.80	9	5.3	1.71	193	60	34.1	1.76	12	8.3	1.45	4	1.7	2.36
	never consulted	1139	1135			31			1139	201			49			10		
Total	ever consulted	1240	964	1044.3	0.92	18	16.9	1.07	1244	394	253.8	1.55	106	92.2	1.15	39	10.8	3.60
	never consulted	6387	5379			87			6422	1310			476			56		
	SER (95% CI)		**0.92**	**(0.86, 0.98)**		**1.07**	**(0.57, 1.56)**			**1.55**	**(1.40, 1.70)**		**1.15**	**(0.93, 1.37)**		**3.60**	**(2.46, 5.72)**	

Table 8.13: Ratio of observed/expected events (ever experienced) according to infertility status (ever TTP of ≥12 months) (Stage 2)

Age at survey		N	ever livebirth O	ever livebirth E	ever livebirth (O/E)	ever stillbirth O	ever stillbirth E	ever stillbirth (O/E)		ever miscarriage O	ever miscarriage E	ever miscarriage (O/E)	ever termination O	ever termination E	ever termination (O/E)	ever ectopic O	ever ectopic E	ever ectopic (O/E)
15-29	≥1 TTP 12mths+	51	49	51.0	0.96	1	0.4	2.28	54	15	11.8	1.27	4	3.9	1.03	1	0.7	1.34
	All TTP <12mths	349	349			3			361	79			26			5		
30-34	≥1 TTP 12mths+	128	128	124.3	1.03	1	0.3	3.60	128	35	32.0	1.09	8	11.6	0.69	1	1.4	0.73
	All TTP <12mths	922	895			2			937	234			85			10		
35-39	≥1 TTP 12mths+	242	233	237.9	0.98	3	3.9	0.77	244	94	55.2	1.70	17	20.7	0.82	10	2.7	3.71
	All TTP <12mths	1175	1155			19			1176	266			100			13		
40-44	≥1 TTP 12mths+	213	208	211.6	0.98	2	1.6	1.21	213	75	48.5	1.55	17	17.7	0.96	13	2.1	6.30
	All TTP <12mths	1033	1026			8			1033	235			86			10		
45-49	≥1 TTP 12mths+	173	167	172.0	0.97	6	3.1	1.95	173	59	34.1	1.73	9	10.9	0.83	6	1.0	5.85
	All TTP <12mths	843	838			15			843	166			53			5		
50-54	≥1 TTP 12mths+	187	185	186.2	0.99	7	6.1	1.14	187	65	35.3	1.84	9	9.0	1.00	4	1.8	2.18
	All TTP <12mths	917	913			30			917	173			44			9		
Total	≥1 TTP 12mths+	994	970	982.0	0.99	20	14.6	1.37	999	343	218.7	1.57	64	74.7	0.86	35	9.9	3.55
	All TTP <12mths	5239	5176			77			5267	1153			394			52		
	SER (95% CI)		0.99	(0.93, 1.05)		1.37	(0.77, 1.97)			1.57	(1.40, 1.73)		0.86	(0.65, 1.07)		3.55	(2.37, 4.72)	

Table 8.14: The proportion of women conceiving a pregnancy and a live birth subsequent to fertility treatment among all women reporting having received fertility treatment, by age at first consultation (Stage 2)

Age of woman at first consultation[1]		Conceived a pregnancy after treatment		Achieved a live birth after treatment	
	N	n	(%)	n	(%)
≤24	137	132	(96.4)	131	(95.6)
25-29	226	213	(94.2)	209	(92.5)
30-34	136	125	(91.9)	125	(91.9)
35-39	65	53	(81.5)	53	(81.5)
≥40	15	13	(86.7)	12	(80.0)
All women	579	536	(92.6)	530	(91.5)

[1] Excluded from this table are 37 women who reported receiving infertility treatment but did not provide date of their first consultation

Chapter 9: National Women's Health Study - Results 2

This chapter contains the results of the detailed investigation of NWHS, addressing the following specific objectives:

- To explore the timing of secondary infertility in terms of ever and prior reproductive events
- To determine whether prior adverse reproductive events are associated with the risk of secondary infertility.

9.1 CHARACTERISTICS OF PREGNANCY ATTEMPTS AND PREGNANCIES

As described in Chapter 7, analyses looking at the association between reproductive outcomes and secondary infertility either used pregnancies or pregnancy attempts as the unit of analysis, depending on the definition of infertility used. Stage 2 data were used for these analyses.

9.1.1 Characteristics of pregnancy attempts

A pregnancy-attempt based analysis was used for the focus on self-reported secondary infertility. The characteristics of all 18,596 pregnancy attempts reported by 7,702 women in the NWHS stage 2 sample are presented in Table 9.1. One hundred and forty-five pregnancy attempts were excluded from this table as they were attributable to 44 women who had specified that they had experienced problems trying to get pregnant, but failed to report the date (or estimated date) when these problems first occurred. All pregnancy attempts (including first pregnancy attempts) remaining after this initial exclusion are included in the table.

Eight percent of pregnancy attempts were characterised by an episode of self-reported infertility, with the highest number occurring in the first pregnancy attempt (13%) and decreasing in each subsequent attempt, to three percent in the fourth or subsequent pregnancy attempts. The vast majority (98%) of pregnancy attempts resulted in a conception, with the highest proportion failing to end in conception occurring in first

pregnancy attempts (2.4%). Age at pregnancy attempt showed a clear and expected association with pregnancy attempt order. Eighteen percent of first pregnancy attempts and only 0.1% of fourth or subsequent pregnancy attempts were associated with women below the age of 20, whereas the figures for women aged 40 and over were 0.2% and 7.6% respectively. The year of pregnancy attempt also showed clear trends, with a higher proportion of later ordered pregnancy attempts occurring in recent years.

9.1.2 Characteristics of pregnancies

For the analysis using a TTP of 12 months or more as an indicator of secondary infertility, a pregnancy-based analysis was used. Table 9.2 displays the characteristics of all 18,390 pregnancies (including first pregnancies) reported by 7508 women, by pregnancy order and before exclusions. Whilst four-fifths of all the reported pregnancies ended in a livebirth, this proportion varied according to pregnancy order. A similarly high proportion of live births was reported for first, second and third pregnancies (peaking at 85% for second pregnancies), but this proportion fell to 72% for fourth and subsequent pregnancies. The frequency of both first and second trimester miscarriages increased with pregnancy order. Termination for non-medical reasons was much higher (5%) in first pregnancies than in later pregnancies. Stillbirths, ectopic pregnancies, molar pregnancies and terminations for medical reasons represented only a very small proportion of pregnancies, and rates for all these outcomes were similar across pregnancies of different order.

Of all pregnancies ending in a live birth, 5.1% ended in the birth of a low birthweight infant (<2500 grams for a singleton; <1500 grams for a multiple) and 5.7% in an infant born before 'term' gestation (<37 weeks for a singleton; <32 weeks for a multiple). The relationship between pregnancy order and both low birthweight and preterm birth represented a U-shaped association, with a higher risk of such outcomes in first pregnancies, lowest in second pregnancies and then rising again with each subsequent pregnancy.

The vast majority (85%) of reported pregnancies occurred in women aged 20-34. As with the previous table focusing on pregnancy attempts, pregnancy order increased with

rising age. Pregnancies were distributed fairly equally across year groups, with later pregnancies more likely to occur in recent years.

For planned pregnancies where a TTP was reported, 59% of pregnancies were conceived in less than three months, and in 11% a conception delay of 12 months or more was reported. Conception delay of at least 12 months was most frequently reported in first pregnancies, with fourth and subsequent pregnancies most likely to be conceived within three months (64% vs. 55% for first pregnancies). Over half of second or subsequent pregnancies occurred within an interval of less than 24 months between the index pregnancy and the directly preceding pregnancy.

9.2 PAST ADVERSE REPRODUCTIVE EVENTS AND SECONDARY INFERTILITY

9.2.1 Self-reported secondary infertility

Selection of sample

The process by which the sample for the focus on self-reported secondary infertility was reached is presented in Figure 9.1. The beginning of this process was characterised by the ordering of pregnancy attempts across a woman's reproductive lifetime. At this point, 145 pregnancy attempts attributable to 44 women were excluded, as these women had reported problems trying to get pregnant but had not given a date (exact or approximate) as to when these problems first occurred. It was therefore not possible to ascertain where in the woman's reproductive career the infertility had first occurred. Next, 7658 pregnancy attempts attributable to 1505 women were excluded as they were first pregnancy attempts and the sample was restricted to second or subsequent attempts to allow for the investigation of least one previous pregnancy outcome on secondary infertility. Just over one thousand pregnancy attempts (1060 attempts, 464 women) beginning after 01/11/99 were excluded to minimise the likelihood of truncation bias. One hundred and twenty-three pregnancy attempts (63 women) were excluded as women had not specified whether they had ever experienced problems getting pregnant. Finally, because this was a single-outcome analysis (in the NWHS questionnaire women were only asked when any problems *first* occurred), 1049 pregnancy attempts attributable to 500 women were censored after the first episode of infertility. Overall,

8706 pregnancy attempts occurring to 5126 women were included in the final sample for this analysis.

Self-reported secondary infertility by age, year and number of previous pregnancy attempts

Overall, 412 (4.7%) pregnancy attempts were characterised by self-reported secondary infertility. The association between selected risk factors and this measure of infertility is presented in Table 9.3. The proportion of pregnancy attempts characterised by this type of infertility rises in a (almost) linear fashion with age at the start of pregnancy attempt (test for trend $p<0.001$). Just over three percent of pregnancy attempts experienced by women aged under 20 were associated with self-reported secondary infertility, with this proportion rising to 12% for women aged 40 or over. Using ages 25-29 as the baseline category, this increase among older age groups was a statistically significant association (p0.04 for 30-34, $p<0.001$ for 35-39 and $\geq$40).

The proportion of pregnancy attempts characterised by self-reported secondary infertility also increased with calendar time (test for trend $p<0.001$), with 7% of attempts in 1995-99 associated with this type of infertility compared to 3% of attempts occurring before 1980. Using the earliest category (<1980) as a baseline, this increase was statistically significant for all five yearly intervals since 1985. The highest proportion of self-reported secondary infertility (5.4%) occurred in second pregnancy attempts (i.e. where there was only one prior pregnancy attempt).

History of reproductive events by number of previous pregnancy attempts

The history of specific pregnancy outcomes is presented in Table 9.4 according to the number of previous pregnancy attempts. Taking second pregnancy attempts as an example, 81% of previous (in this case first) pregnancy attempts resulted in a live birth. Ten percent ended in miscarriage, one percent ended with a stillbirth, 0.4% ended in an ectopic pregnancy, and eight percent and five percent resulted in the birth of a low birthweight baby and a preterm delivery respectively.

Not surprisingly, the likelihood that a woman had experienced any adverse outcomes increased with the number of previous pregnancy attempts. However, looking

specifically at what happened in the last pregnancy, the pattern is less clear in some cases. The proportion of last pregnancies which ended in a termination was highest (7.3%) when there had only been one previous pregnancy attempt. This proportion fell considerably when there had been 2 or 3 prior pregnancy attempts (3.5% and 3.6% respectively), before rising slightly to 4.2% for pregnancy attempts with between 4-13 prior pregnancy attempts. The likelihood of a miscarriage occurring in the last pregnancy rose considerably with pregnancy attempt order – 10% where there had only been one past pregnancy attempt and 37% where there had been four or more previous pregnancy attempts. The rate of ectopic pregnancy in the last pregnancy attempt varied very slightly with pregnancy attempt order with a small increase from 0.4% where there was one prior pregnancy attempt to 1.2% for four or more. The likelihood of the last pregnancy ending in a low birthweight or preterm delivery was highest for both second pregnancy attempts and fourth or subsequent pregnancy attempts. The proportion of last pregnancies that ended in a livebirth fell dramatically from 81% where there had been one previous pregnancy attempt to 55% when there had been four or more.

Association between past adverse outcomes and self-reported secondary infertility: crude analyses

Crude odds ratios summarising the association between past adverse outcomes and self-reported infertility are presented in Table 9.5. For most outcomes under study, a history of the adverse outcome in either a past or the directly preceding pregnancy attempt increased the risk of self-reported infertility in the current pregnancy attempt. This was particularly true for a past history of termination (all, and separated into clinically-indicated and non-clinically indicated), where all crude odds ratios were above 2.00 and statistically significant at $p < 0.05$. The proportion of those reporting self-reported infertility was slighter higher (and statistically significantly so) where a past history of miscarriage was evident, this trend remained for first trimester miscarriage but disappeared when only second trimester miscarriages were considered. Crude results showed little or no association between a past history of stillbirth, low birthweight or preterm delivery, and self-reported infertility. A prior history of ectopic pregnancy was associated with self-reported infertility in the index pregnancy attempt, with an odds ratio of 3.70 for an ectopic pregnancy in a past pregnancy and 4.81 for ectopic

pregnancy in the directly preceding pregnancy (95% CI 2.02-6.78 and 2.47-9.38 respectively).

Association between past adverse outcomes and self-reported secondary infertility: adjusted analyses

Odds ratios for the association between individual past adverse outcomes and self-reported infertility were adjusted for potential confounders (Table A.2.3, Appendix 2). Age of the women and year of pregnancy attempt were considered important *a priori* confounders, and although adjusting for these variables did not always change the odds ratio by a margin of >10%, there were changes to the p values and these variables were kept in the model for completeness. The effect of adjusting for a history of ectopic pregnancy was investigated with respect to summary measures for effect of past adverse outcomes (other than ectopic pregnancy) on self-reported infertility. These adjusted odds ratios were practically identical to those adjusting only for age and year, so this variable was not included in the final adjusted model. Odds ratios including adjustment for a history of ectopic pregnancy are contained in Table A.2.4 (Appendix 2).

The final odds ratios summarising the association between past adverse outcomes and self-reported secondary infertility, adjusted for age and year, are presented in Table 9.5. Termination in any past pregnancy and termination in the last pregnancy both significantly increased the likelihood of self-reported infertility in the index pregnancy attempt by over two-fold (OR 2.08, 95% CI 1.60-2.70; OR 2.81, 95% CI 2.09-3.78). This statistically significant increase persisted for a past history of clinical indicated termination (OR 2.17, 95% CI 1.06-4.45), but where a clinically indicated termination had occurred in the last pregnancy the OR lost statistical significance. There was a strong association between non-clinically indicated termination and self-reported infertility, with this outcome in any past pregnancy increasing the likelihood of self-reported infertility in the current pregnancy to an OR of 2.02 (95% CI 1.54-2.65), increased even further to where such a termination had occurred in the directly preceding pregnancy (OR 2.84, 95% CI 2.08-3.87). A history of miscarriage was associated with an elevated risk of infertility only where the miscarriage had occurred in the directly preceding pregnancy (OR 1.37, 95% CI 1.07-1.77); the effect of miscarriage in any previous pregnancy did not retain significance after adjustment (OR 1.22, 95% CI

0.96-1.53). These results were reflected where there was a history of first trimester miscarriage: this outcome in the last pregnancy was associated with an increased risk of infertility (OR 1.48, 95% CI 1.13-1.93) but this trend was not repeated where the first trimester miscarriage occurred in any previous pregnancy. As with the crude results, a history of second trimester miscarriage or stillbirth was not associated with infertility. The strongest effect of past outcomes were seen for a history of ectopic pregnancy, with such an outcome in any previous pregnancy or the last pregnancy both strongly associated with an increased risk of self-reported infertility (OR 3.37, 95% CI 1.75-6.48; OR 4.76, 95% CI 2.38-9.53). A history of either low birthweight or preterm delivery was not associated with the risk of self-reported infertility.

9.2.2 TTP-based infertility

Figure 9.2 shows the process by which the final sample for this analysis was reached. Of 18,741 pregnancy attempts originally reported, 7710 pregnancy attempts attributable to 1520 women were excluded as they were first pregnancy attempts rather than the second or subsequent pregnancy attempts which were the focus of the analysis. Pregnancy attempts beginning on or after 01/11/99 were then excluded in order to minimise bias (1095 pregnancy attempts excluded, 465 women). Eighty-seven pregnancy attempts (60 women) were excluded as the pregnancy attempt did not result in a pregnancy. Of the remaining 9849 pregnancies, 2726 (833 women) were excluded as the pregnancy was reported as 'unplanned', and a further 908 pregnancies (561 women) were excluded because, although the pregnancy was reported as 'planned', no TTP was provided. This left a final sample available for analysis of 6215 pregnancies occurring to 5413 women.

TTP and pregnancy outcome

Table 9.6 contains information on the outcome of the index pregnancy by TTP. The vast majority of pregnancies ended in a livebirth, but the proportion decreased linearly with TTP. Eight-eight percent of pregnancies that were conceived within three months of trying ended in a live birth, compared to 76% of pregnancies that took 12 months or more to conceive. The very small number of stillbirths, termination for clinical reasons, and molar pregnancies varied little by TTP. The proportion of pregnancies ending in first trimester miscarriage rose with TTP, with eight percent and 16% of pregnancies conceived in less than 3 months and 12 months or more ending in this way respectively.

Around 2-3% of pregnancies ended in a second trimester miscarriage, and this proportion varied little by TTP. Unsurprisingly, there were no terminations for non-clinical reasons in this cohort of planned pregnancies.

For both low birthweight and preterm birth, the highest proportions of pregnancies resulting in this outcome occurred in pregnancies that took 12 months or more to conceive. Asides from the elevated risk associated with those that took longest to conceive, there were no clear-cut trends with respect to TTP.

Time to pregnancy according to use of fertility treatment, age, year and previous pregnancies

Time to pregnancy categorised by the use of fertility treatment, age of the woman, year of pregnancy and the number of previous pregnancies is reported in Table 9.7. As expected, there was an extremely strong association between TTP and the use of fertility treatment to conceive a pregnancy. Compared to spontaneously conceived pregnancies, pregnancies conceived by fertility treatment were more than 20 times as likely to be associated with a conception delay of 12 months or more. There was a slight trend between TTP and age (p value for trend 0.005), although individual odds ratios stratified by age did not show significant association. The association between year of conception and TTP was somewhat inconsistent, with only pregnancies occurring during the interval 1980-84 associated with a slightly increased proportion of conceptions of $\geq$ 12 months compared to the reference category of conceptions <1980. Looking at the number of previous pregnancies, the only statistically significant association was a slightly elevated proportion of TTP $\geq$ 12 months or more among those with two previous pregnancies compared to the reference category of one previous pregnancy.

History of reproductive events by number of previous pregnancies

The proportion of pregnancies with a history of specific pregnancy outcomes is presented according to the number of previous pregnancies in Table 9.8. This table differs from a similar table presented earlier (Table 9.4) by using the number of previous *pregnancies* as the denominator rather than the number of previous *pregnancy attempts*. As expected, the proportion with a history of each outcome in any past pregnancy increased according to the number of previous pregnancies. For example, there was a history of termination in five percent of index pregnancies where there had been only

one previous pregnancy, rising to 20% where there had been four or more previous pregnancies. Terminations occurred in 3-5%, of last pregnancies with a slightly higher proportion occurring where there had been only one previous pregnancy (where the index pregnancy was a second pregnancy). The risk of miscarriage in the last pregnancy rose steeply according to the number of previous pregnancy attempts, with the risk at 13% where there had only been one previous pregnancy rising to 49% where there were four or more previous pregnancies. With both stillbirth and ectopic pregnancies, numbers of events are small and no clear trends are apparent. The risk of low birthweight and preterm delivery appeared to decrease slightly with the number of previous pregnancies, with 4.2% and 4.6% of second pregnancies ending in low birthweight and/or preterm delivery, decreasing to 2.7% and 3.0% respectively where there had been four or more previous pregnancies. The proportion of last pregnancies ending in livebirth fell dramatically with increasing pregnancies, 82% of second pregnancies followed a livebirth, but only 42% of fourth or subsequent pregnancies.

Association between past adverse outcomes and TTP-based secondary infertility: crude analyses

The crude results for associations between past adverse outcomes and secondary infertility characterised by TTP ≥12 months are presented in Table 9.9. Although for many exposures, those experiencing the adverse outcome in either a past or the last pregnancy reported a higher risk of TTP-based infertility in the index pregnancy, this trend was not consistent, and only a few odds ratios were statistically significant. Having experienced a clinically indicated termination in any past pregnancy was associated with TTP based infertility, but although an elevated ratio was observed where the clinically indicated termination occurred in the last pregnancy, the measure of effect was not significant. There were no significant associations between terminations overall (any type) or non-clinical indicated termination in either the last pregnancy or any previous pregnancy. Miscarriage in any past pregnancy was associated with a significantly increased risk of TTP-based infertility, and this trend persisted when the analysis was stratified to look at first trimester miscarriages only. The odds ratios for both miscarriage and first trimester miscarriage in the last pregnancy suggested an increase in the risk of infertility, but this did not reach statistical significance. The crude results provided little evidence for an association between second trimester miscarriage and TTP-based

infertility. The odds ratios suggested that a history of stillbirth increased the risk of TTP-based infertility, but this trend was not statistically significant. There was a strong association between a history of ectopic pregnancy and TTP based infertility, with ectopic pregnancy in any previous pregnancy or the directly preceding pregnancy increasing the risk of a delayed conception in the index pregnancy nearly fourfold. There was little evidence for any association between low birthweight and TTP-based infertility. A history of preterm delivery in either any previous or the last pregnancy appears associated with the risk of TTP based infertility, increasing the odds ratio to 1.41 (95% CI 1.00-1.98) and 1.70 (95% CI 1.16, 2.47) respectively.

Association between past adverse outcomes and TTP-based secondary infertility: adjusted analyses

All associations were adjusted for the *a priori* confounders age and year of pregnancy. These variables changed the estimates very little but were kept in for completeness. The effect of adjusting for the number of previous pregnancies was also explored. These results are presented in Table A.2.5 (Appendix 2). Again, adjusting for this variable resulted in only minor fluctuations in the estimates; the decision not to include this in the final model was taken due to the known correlation between past outcomes and the number of previous pregnancies. As explained in Chapter 7, ectopic pregnancy was also considered an important potential confounder due to the strong association between ectopic pregnancy and impaired fertility. Odds ratios for exposures other than ectopic pregnancy, adjusted for a history of ectopic pregnancy were calculated. These estimates differed only marginally and were not included in the final model. These results are presented in Table A.2.6 (Appendix 2).

The final adjusted models for associations between past adverse outcomes and TTP-based secondary infertility are presented in Table 9.9. After adjustment for age and year of pregnancy, both associations between miscarriage in any past pregnancy and TTP-based infertility, and first trimester miscarriage in any past pregnancy and TTP-based infertility, lost significance. Only associations between TTP-based infertility and the following exposures remained statistically significant after adjustment: a history of clinically indicated termination in any past pregnancy (OR 2.31, 95% CI 1.07-4.98), ectopic pregnancy in either the last or any previous pregnancy (OR 3.72, 95% CI 2.26-

6.14; OR 3.65, 95% CI 2.00, 6.64), and preterm delivery in the last pregnancy (OR 1.71, 95% CI 1.18-2.50). There was little evidence to support associations between other exposures and secondary infertility characterised in this way, although some associations did continue to show a non-statistically significant increase (notably any miscarriage and first trimester miscarriage).

Finally, the role of fertility treatment was explored in relation to the association between past adverse outcomes and TTP-based secondary infertility. It had been decided not to consider the use of fertility treatment as a potential confounder, but to do a sub-analysis applying the final model to a sample excluding all 165 pregnancies conceived as a result of fertility treatment. The results of this analysis are reported in Table A.2.7 (Appendix 2). This analysis confirmed most associations in terms of trend and strength, except for the previously significant association between clinically indicated terminations and infertility. The two odds ratios reporting the association between clinically indicated termination in any past pregnancy and the last pregnancy showed a dramatic reduction towards unity after fertility treatment associated pregnancies were excluded. This was due to the proportionately high number of pregnancies resulting from treatment observed among pregnancies with a TTP $\geq$12 months where the last or any previous pregnancy ended in a clinically-indicated termination. Five of 13 pregnancies with a previous clinically indicated termination and a long TTP were excluded for this reason, and 5/6 pregnancies taking $\geq$ 12 months to conceive where the last pregnancy resulted in a clinically indicated termination.

Table 9.1: Characteristics of pregnancy attempts, by pregnancy attempt order (before exclusions)

	All pregnancy attempts		Pregnancy attempt order							
	All		1		2		3		4-13	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
PREGNANCY ATTEMPTS (N=18,596)[1]										
Self-reported infertility										
Yes	1442	(7.8)	973	(12.8)	304	(5.0)	111	(3.8)	54	(3.0)
No	16951	(92.2)	6606	(87.2)	5786	(95.0)	2807	(96.2)	1752	(97.0)
Missing	203		79		63		33		28	
Attempt resulted in conception										
Yes	18289	(98.3)	7471	(97.6)	6076	(98.7)	2926	(99.2)	1816	(99.0)
No	307	(1.7)	187	(2.4)	77	(1.3)	25	(0.8)	18	(1.0)
Age of woman at pregnancy attempt										
<20	1741	(9.4)	1373	(17.9)	329	(5.3)	38	(1.3)	1	(0.1)
20-24	4820	(25.9)	2629	(34.3)	1537	(25.0)	500	(16.9)	154	(8.4)
25-29	6577	(35.4)	2562	(33.5)	2460	(40.0)	1059	(35.9)	496	(27.0)
30-34	3960	(21.3)	907	(11.8)	1431	(23.3)	960	(32.5)	662	(36.1)
35-39	1258	(6.8)	169	(2.2)	362	(5.9)	346	(11.7)	381	(20.8)
≥40	240	(1.3)	18	(0.2)	34	(0.6)	48	(1.6)	140	(7.6)
Year of pregnancy attempt										
<1980	4040	(21.7)	2082	(27.2)	1321	(21.5)	463	(15.7)	174	(9.5)
1980-84	2640	(14.2)	1137	(14.8)	880	(14.3)	391	(13.2)	232	(12.6)
1985-89	3118	(16.8)	1307	(17.1)	1031	(16.8)	494	(16.7)	286	(15.6)
1990-94	3504	(18.8)	1412	(18.4)	1124	(18.3)	586	(19.9)	382	(20.8)
1995-99	4003	(21.5)	1392	(18.2)	1384	(22.5)	729	(24.7)	498	(27.2)
2000-02	1291	(6.9)	328	(4.3)	413	(6.7)	288	(9.8)	262	(14.3)

[1]44 women (145 pregnancy attempts) were excluded from all pregnancy-attempt based analyses as they had reported problems trying to get pregnant but had not given the date (or estimated date) that these problems first occurred. More information on these women is reported in Appendix 2

Table 9.2: Characteristics of pregnancies, by pregnancy order (before exclusions)

	All pregnancies		Pregnancy order							
	All		1		2		3		4-13	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
PREGNANCIES (N=18,390)										
Outcome of pregnancy										
Livebirth	14831	(82.2)	6134	(82.5)	5113	(85.3)	2305	(80.6)	1279	(72.5)
Stillbirth	113	(0.6)	52	(0.7)	37	(0.6)	12	(0.4)	12	(0.7)
First trimester miscarriage	1906	(10.6)	644	(8.7)	548	(9.1)	366	(12.8)	348	(19.7)
Second trimester miscarriage	420	(2.3)	140	(1.9)	137	(2.3)	88	(3.1)	55	(3.1)
Ectopic	104	(0.6)	38	(0.5)	37	(0.6)	17	(0.6)	12	(0.7)
Termination for medical reasons	90	(0.5)	33	(0.4)	22	(0.4)	21	(0.7)	14	(0.8)
Termination for non-medical reasons	563	(3.1)	387	(5.2)	88	(1.5)	48	(1.7)	39	(2.2)
Molar pregnancy	26	(0.1)	7	(0.1)	11	(0.2)	4	(0.1)	4	(0.2)
Ongoing (current) pregnancy	338		73		112		82		348	
Birthweight[1]										
Low birthweight	732	(5.1)	366	(6.1)	195	(3.9)	101	(4.5)	70	(5.7)
Normal birthweight	13734	(94.9)	5655	(93.9)	4785	(96.1)	2144	(95.5)	1150	(94.3)
Missing	365		113		133		60		59	
Gestation[1]										
Preterm birth	850	(5.7)	379	(6.2)	233	(4.6)	132	(5.7)	106	(8.3)
Term	13981	(94.3)	5755	(93.8)	4880	(95.4)	2173	(94.3)	1173	(91.7)
Age of woman at end of pregnancy										
<20	911	(6.1)	756	(11.7)	143	(2.8)	12	(0.5)	0	(0.0)
20-24	3357	(22.6)	1859	(28.7)	1109	(21.7)	318	(13.8)	71	(5.6)
25-29	5439	(36.7)	2041	(31.5)	2041	(39.9)	792	(34.4)	321	(25.1)
30-34	3768	(25.4)	1425	(22.0)	1425	(27.9)	830	(36.0)	508	(39.7)
35-39	1188	(8.0)	359	(5.5)	359	(7.0)	314	(13.6)	300	(23.5)
≥40	168	(1.1)	36	(0.6)	36	(0.7)	39	(1.7)	79	(6.2)
Year of pregnancy end										
<1980	3008	(20.3)	1545	(25.2)	1013	(19.8)	336	(14.6)	114	(8.9)
1980-84	2232	(15.0)	920	(15.0)	795	(15.5)	333	(14.4)	184	(14.4)
1985-89	2467	(16.6)	1004	(16.4)	854	(16.7)	396	(17.2)	213	(16.7)
1990-94	2815	(19.0)	1110	(18.1)	962	(18.8)	472	(20.5)	271	(21.2)
1995-99	3044	(20.5)	1143	(18.6)	1054	(20.6)	523	(22.7)	324	(25.3)
2000-02	1265	(8.5)	412	(6.7)	435	(8.5)	245	(10.6)	173	(13.5)
Pregnancy conceived as a result of fertility treatment										
No	17957	(97.7)	7304	(97.3)	5975	(97.9)	2880	(97.9)	1798	(98.0)
Yes	431	(2.3)	203	(2.7)	130	(2.1)	62	(2.1)	36	(2.0)
Time to pregnancy[2]										
<3 months	6679	(59.3)	2434	(54.8)	2605	(62.0)	1052	(61.8)	588	(64.0)
3 - <6 months	2354	(20.9)	926	(20.9)	902	(21.5)	352	(20.7)	174	(18.9)
6 - <12 months	1029	(9.1)	433	(9.8)	371	(8.8)	140	(8.2)	85	(9.2)
≥ 12 months	1204	(10.7)	647	(14.6)	327	(7.8)	158	(9.3)	72	(7.8)
Inter-pregnancy interval[3]										
<6 months	1310	(12.0)	-		522	(8.6)	413	(14.0)	375	(20.4)
6 - <12 months	1611	(14.8)	-		831	(13.6)	422	(14.3)	358	(19.5)
12 - <24 months	3212	(29.5)	-		2031	(33.3)	744	(25.3)	437	(23.8)
24 - <48 months	2870	(26.4)	-		1757	(28.8)	762	(25.9)	351	(19.1)
> 48 months	1879	(17.3)	-		964	(15.8)	602	(20.5)	313	(17.1)

[1]Livebirths only
[2]Planned pregnancies for which a TTP was provided only
[3]Interval between end of last pregnancy and conception of current pregnancy

Figure 9.1: Flowchart showing selection of sample for analysis of self-reported infertility

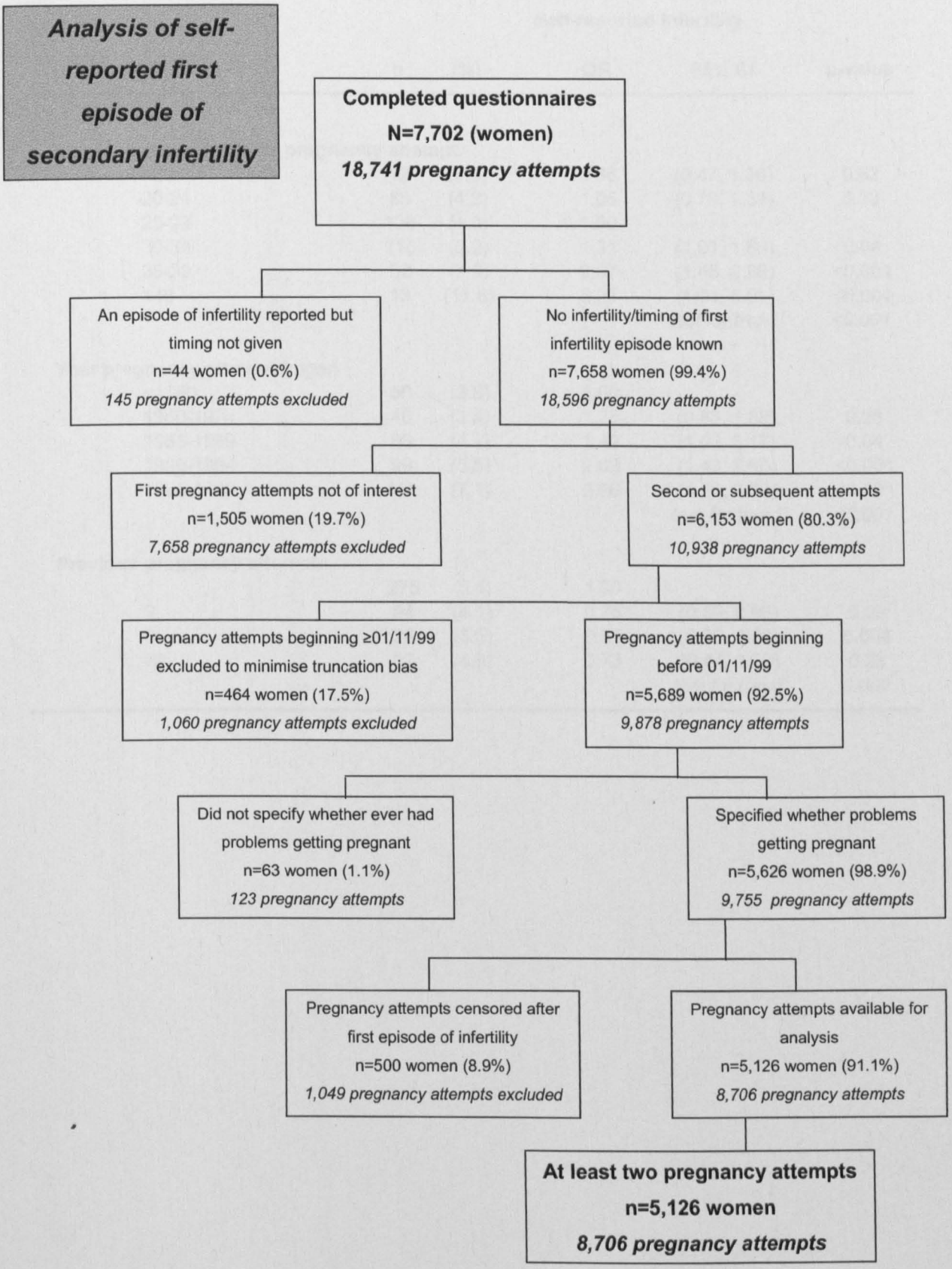


Table 9.3: Self-reported secondary infertility by selected risk factors

			Self-reported infertility		
	n	(%)	OR	95% CI	p-value
Age of woman at start of pregnancy attempt					
<20	12	(3.5)	0.86	(0.47, 1.56)	0.62
20-24	83	(4.2)	1.05	(0.79, 1.39)	0.73
25-29	136	(4.0)	1.00	-	
30-34	116	(5.2)	1.31	(1.01, 1.69)	0.04
35-39	52	(7.9)	2.07	(1.48, 2.88)	<0.001
≥40	13	(11.8)	3.21	(1.71, 6.01)	<0.001
				test for trend	*<0.001*
Year pregnancy attempt began					
<1980	50	(2.8)	1.00		
1980-1984	46	(3.4)	1.25	(0.83, 1.88)	0.28
1985-1989	66	(4.1)	1.49	(1.02, 2.17)	0.04
1990-1994	99	(5.5)	2.02	(1.43, 2.86)	<0.001
1995-1999	151	(7.1)	2.66	(1.92, 3.69)	<0.001
				test for trend	*<0.001*
Previous pregnancy attempts					
1	275	(5.4)	1.00		
2	94	(4.1)	0.75	(0.59, 0.96)	0.02
3	26	(3.0)	0.55	(0.36, 0.82)	0.004
≥4	17	(4.0)	0.73	(0.44, 1.22)	0.23
				test for trend	*0.002*

Table 9.4: History of reproductive events by number of previous pregnancy attempts

			Number of previous pregnancy attempts							
			1		2		3		4-13	
			n	(%)	n	(%)	n	(%)	n	(%)
TERMINATION	**In any past pregnancy**	Yes	376	(7.3)	291	(12.7)	141	(16.3)	88	(20.7)
		No	4750	(92.7)	1999	(87.3)	723	(83.7)	338	(79.3)
	In last pregnancy	Yes	376	(7.3)	81	(3.5)	31	(3.6)	18	(4.2)
		No	4750	(92.7)	2209	(96.5)	833	(96.4)	408	(95.8)
MISCARRIAGE	**In any past pregnancy**	Yes	509	(9.9)	704	(30.7)	441	(51.0)	292	(68.5)
		No	4617	(90.1)	1586	(69.3)	423	(49.0)	134	(31.5)
	In last pregnancy	Yes	509	(9.9)	412	(18.0)	219	(25.3)	158	(37.1)
		No	4617	(90.1)	1878	(82.0)	645	(74.7)	268	(62.9)
STILLBIRTH	**In any past pregnancy**	Yes	44	(0.9)	52	(2.3)	36	(4.2)	34	(8.0)
		No	5082	(99.1)	2238	(97.7)	828	(95.8)	392	(0.0)
	In last pregnancy	Yes	44	(0.9)	20	(0.9)	8	(0.9)	10	(2.3)
		No	5082	(99.1)	2270	(99.1)	856	(99.1)	416	(0.0)
ECTOPIC PREGNANCY	**In any past pregnancy**	Yes	22	(0.4)	31	(1.4)	23	(2.7)	16	(3.8)
		No	5104	(99.6)	2259	(98.6)	841	(97.3)	410	(0.0)
	In last pregnancy	Yes	22	(0.4)	20	(0.9)	11	(1.3)	5	(1.2)
		No	5104	(99.6)	2270	(99.1)	853	(98.7)	421	(98.8)
LOW BIRTHWEIGHT	**In any past pregnancy**	Yes	254	(5.0)	185	(8.1)	85	(9.8)	55	(12.9)
		No	4872	(95.0)	2105	(91.9)	779	(90.2)	371	(87.1)
	In last pregnancy	Yes	254	(5.0)	85	(3.7)	23	(2.7)	18	(4.2)
		No	4872	(95.0)	2205	(96.3)	841	(97.3)	408	(95.8)
PRETERM DELIVERY	**In any past pregnancy**	Yes	250	(4.9)	178	(7.8)	100	(11.6)	65	(15.3)
		No	4876	(95.1)	2112	(92.2)	764	(88.4)	361	(84.7)
	In last pregnancy	Yes	250	(4.9)	91	(4.0)	37	(4.3)	23	(5.4)
		No	4876	(95.1)	2199	(96.0)	827	(95.7)	403	(94.6)
LIVEBIRTH	**In any past pregnancy**	Yes	4169	(81.3)	2143	(93.6)	842	(97.5)	425	(99.8)
		No	957	(18.7)	147	(6.4)	22	(2.5)	1	(0.2)
	In last pregnancy	Yes	4169	(81.3)	1750	(76.4)	594	(68.8)	233	(54.7)
		No	957	(18.7)	540	(23.6)	270	(31.3)	193	(45.3)

Table 9.5: Summary table for the association between past adverse outcomes and self-reported secondary infertility

		Pregnancy attempts	Episode of self-reported infertility in current pregnancy attempt			
		N	n	%	Crude OR (95% CI)	Adjusted OR (95% CI)[1]
TERMINATION						
In any past pregnancy	Yes	896	83	(9.3)	**2.32 (1.79, 3.00)**	**2.08 (1.60, 2.70)**
	No	7810	329	(4.2)	1.00	1.00
In last pregnancy	Yes	506	60	(11.9)	**3.00 (2.25, 4.00)**	**2.81 (2.09, 3.78)**
	No	8200	352	(4.3)	1.00	1.00
CLINICALLY INDICATED TERMINATIONS						
In any past pregnancy	*Yes*	*84*	*9*	*(10.7)*	***2.45 (1.21, 4.93)***	***2.17 (1.06, 4.45)***
	No	*8622*	*403*	*(4.7)*	*1.00*	*1.00*
In last pregnancy	*Yes*	*56*	*6*	*(10.7)*	***2.44 (1.03, 5.74)***	*2.17 (0.92, 5.12)*
	No	*8650*	*406*	*(4.7)*	*1.00*	*1.00*
NON-CLINICALLY INDICATED TERMINATIONS						
In any past pregnancy	*Yes*	*822*	*75*	*(9.1)*	***2.25 (1.72, 2.94)***	***2.02 (1.54, 2.65)***
	No	*7884*	*337*	*(4.3)*	*1.00*	*1.00*
In last pregnancy	*Yes*	*450*	*54*	*(12.0)*	***3.01 (2.23, 4.06)***	***2.84 (2.08, 3.87)***
	No	*8256*	*358*	*(4.3)*	*1.00*	*1.00*
MISCARRIAGE						
In any past pregnancy	Yes	1946	114	(5.9)	**1.35 (1.08,1.69)**	1.22 (0.96, 1.53)
	No	6760	298	(4.4)	1.00	1.00
In last pregnancy	Yes	1298	85	(6.5)	**1.52 (1.18, 1.94)**	**1.37 (1.07, 1.77)**
	No	7408	327	(4.4)	1.00	1.00
1st TRIMESTER MISCARRIAGE						
In any past pregnancy	*Yes*	*1571*	*97*	*(6.2)*	***1.42 (1.12, 1.81)***	*1.26 (0.99, 1.61)*
	No	*7135*	*315*	*(4.4)*	*1.00*	*1.00*
In last pregnancy	*Yes*	*1028*	*73*	*(7.1)*	***1.65 (1.27, 2.15)***	***1.48 (1.13, 1.93)***
	No	*7678*	*339*	*(4.4)*	*1.00*	*1.00*
2nd TRIMESTER MISCARRIAGE						
In any past pregnancy	*Yes*	*483*	*20*	*(4.1)*	*0.86 (0.54, 1.37)*	*0.83 (0.52, 1.33)*
	No	*8223*	*392*	*(4.8)*	*1.00*	*1.00*
In last pregnancy	*Yes*	*258*	*12*	*(4.7)*	*0.93 (0.52, 1.68)*	*0.92 (0.51, 1.67)*
	No	*8036*	*400*	*(5.0)*	*1.00*	*1.00*
STILLBIRTH						
In any past pregnancy	Yes	166	7	(4.2)	0.88 (0.42, 1.88)	1.03 (0.47, 2.23)
	No	8540	405	(4.7)	1.00	1.00
In last pregnancy	Yes	82	4	(4.9)	1.03 (0.37, 2.84)	1.26 (0.45, 3.53)
	No	8624	408	(4.7)	1.00	1.00
ECTOPIC PREGNANCY						
In any past pregnancy	Yes	92	14	(15.2)	**3.70 (2.02, 6.78)**	**3.37 (1.75, 6.48)**
	No	8614	398	(4.6)	1.00	1.00
In last pregnancy	Yes	58	11	(19.0)	**4.81 (2.47, 9.38)**	**4.76 (2.38, 9,53)**
	No	8648	401	(4.6)	1.00	1.00
LOW BIRTHWEIGHT						
In any past pregnancy	Yes	579	22	(3.8)	0.78 (0.51, 1.21)	0.81 (0.52, 1.25)
	No	8127	390	(4.8)	1.00	1.00
In last pregnancy	Yes	380	12	(3.2)	0.76 (0.44, 1.31)	0.80 (0.46, 1.38)
	No	8326	398	(4.8)	1.00	1.00
PRETERM DELIVERY						
In any past pregnancy	Yes	593	29	(4.9)	1.04 (0.70, 1.53)	1.00 (0.67, 1.48)
	No	8113	383	(4.7)	1.00	1.00
In last pregnancy	Yes	401	17	(4.2)	0.89 (0.54, 1.45)	0.88 (0.53, 1.45)
	No	8305	395	(4.8)	1.00	1.00

[1]Adjusted for age of woman at pregnancy attempt and year of pregnancy attempt
N.B. Odds ratios in bold are significant at $p<0.05$

Figure 9.2: Flowchart showing selection of sample for analysis of infertility TTP ≥12 months

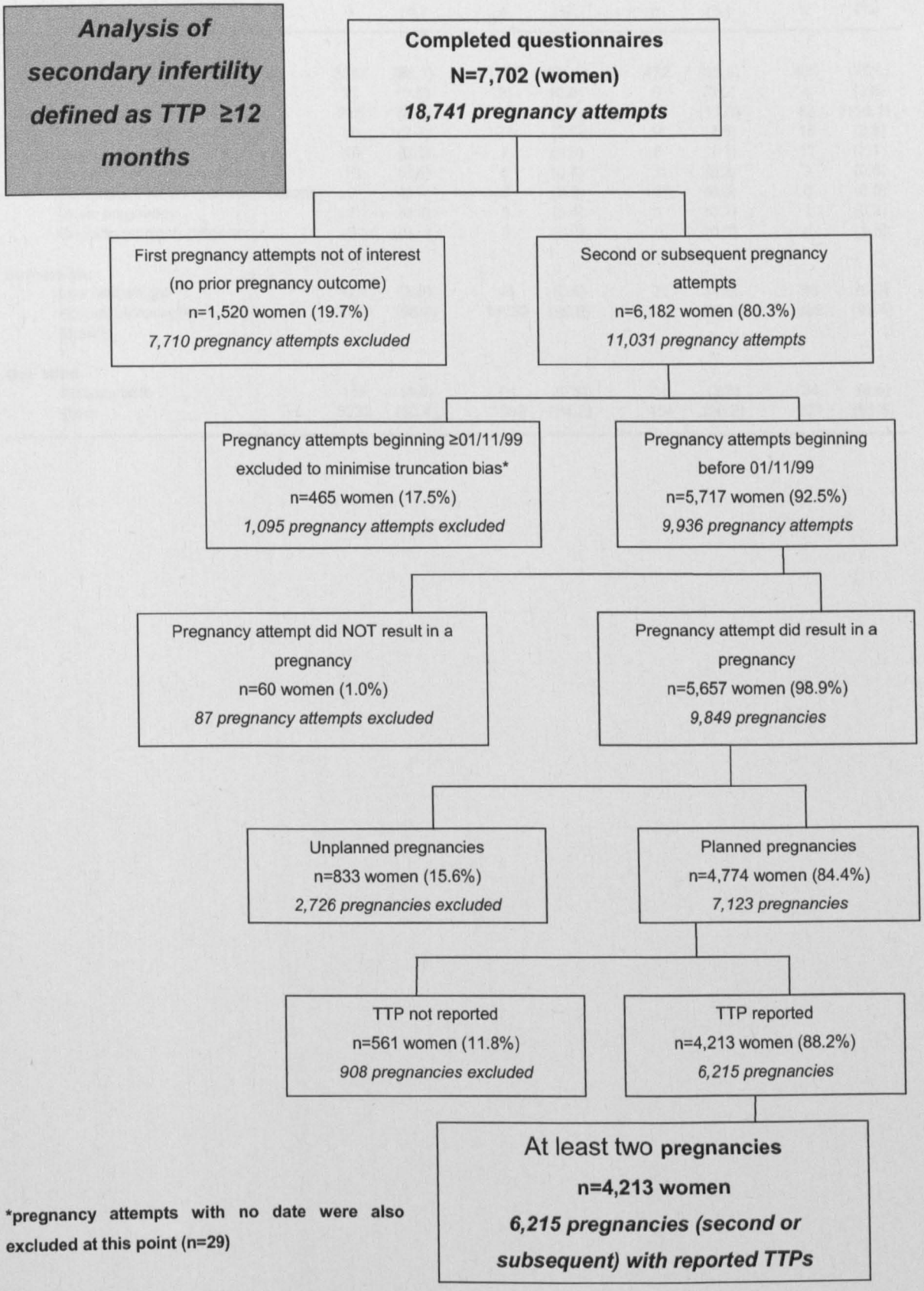


Table 9.6: Time to pregnancy and pregnancy outcome

	Time to pregnancy							
	<3 months		3 - <6 months		6 - <12 months		≥ 12 months	
	n	(%)	n	(%)	n	(%)	n	(%)
Outcome of pregnancy								
Livebirth	3387	(88.1)	1103	(86.1)	472	(85.0)	405	(76.0)
Stillbirth	21	(0.5)	10	(0.8)	0	(0.0)	4	(0.8)
First trimester miscarriage	316	(8.2)	124	(9.7)	61	(11.0)	86	(16.1)
Second trimester miscarriage	89	(2.3)	27	(2.1)	14	(2.5)	15	(2.8)
Ectopic	10	(0.3)	7	(0.5)	6	(1.1)	11	(2.1)
Termination for medical reasons	16	(0.4)	5	(0.4)	1	(0.2)	3	(0.6)
Termination for non-medical reasons	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Molar pregnancy	7	(0.2)	5	(0.4)	1	(0.2)	1	(0.2)
Ongoing (current) pregnancy	0	(0.0)	0	(0.0)	0	(0.0)	8	(1.5)
Birthweight								
Low birthweight	126	(3.8)	44	(0.4)	21	(4.5)	26	(6.6)
Normal birthweight	3173	(96.2)	11032	(99.6)	444	(95.5)	368	(93.4)
Missing								
Gestation								
Preterm birth	155	(4.6)	64	(5.8)	18	(3.8)	34	(8.4)
Term	3232	(95.4)	1039	(94.2)	454	(96.2)	371	(91.6)

Table 9.7: Time to pregnancy according to selected risk factors

		Time to pregnancy								TTP ≥ 12 months vs. TTP < 12 months		
		<3 months		3 - <6 months		6 - <12 months		≥ 12 months		OR	95% CI	p-value
		n	(%)	n	(%)	n	(%)	n	(%)			
Pregnancy conceived as a result of fertility treatment	No	3825	(63.2)	1262	(20.9)	532	(8.8)	431	(7.1)	1.00	-	-
	Yes	21	(12.7)	19	(11.5)	23	(13.9)	102	(61.8)	21.11	(14.93, 29.85)	<0.001
Age of woman at pregnancy attempt												
	<20	96	(61.9)	28	(18.1)	16	(10.3)	15	(9.7)	0.76	(0.41, 1.37)	0.34
	20-24	806	(63.1)	260	(20.3)	117	(9.2)	95	(7.4)	0.75	(0.42, 1.35)	0.35
	25-29	1609	(62.8)	565	(22.0)	197	(7.7)	192	(7.5)	1.00	-	
	30-34	1028	(60.9)	327	(19.4)	167	(9.9)	165	(9.8)	1.01	(0.56, 1.83)	0.97
	35-39	273	(22.9)	816	(68.3)	49	(4.1)	56	(4.7)	1.28	(0.68, 2.43)	0.45
	≥40	34	(50.0)	15	(22.1)	9	(13.2)	10	(14.7)	1.61	(0.61, 4.23)	0.33
											test for trend	*0.005*
Year of pregnancy attempt												
	<1980	767	(63.0)	255	(21.0)	104	(8.5)	91	(7.5)	1.00	-	-
	1980-1984	564	(59.6)	210	(22.2)	74	(7.8)	99	(10.5)	1.44	(1.07, 1.95)	0.02
	1985-1989	683	(63.5)	216	(20.1)	95	(8.8)	82	(7.6)	1.02	(0.74, 1.41)	0.90
	1990-1994	869	(65.1)	263	(19.7)	92	(6.9)	110	(8.2)	1.11	(0.82, 1.50)	0.49
	1995-1999	963	(58.7)	337	(20.5)	190	(11.6)	151	(9.2)	1.25	(0.94, 1.66)	0.12
											test for trend	*0.28*
Previous pregnancies	1	2403	(61.7)	825	(21.2)	351	(9.0)	316	(8.1)	1.00	-	-
	2	935	(61.0)	314	(20.5)	128	(8.4)	155	(10.1)	1.27	(1.06, 1.54)	0.01
	3	339	(64.7)	98	(18.7)	49	(9.4)	38	(7.3)	0.88	(0.83, 1.25)	0.49
	≥4	169	(64.0)	44	(16.7)	27	(10.2)	24	(9.1)	1.13	(0.68, 1.81)	0.63
											test for trend	*0.47*

Table 9.8: History of reproductive events by number of previous pregnancies

			Number of previous pregnancies							
			1		2		3		4-13	
			n	(%)	n	(%)	n	(%)	n	(%)
TERMINATION	**In any past pregnancy**	Yes	212	(5.4)	198	(12.9)	91	(17.4)	53	(20.1)
		No	3683	(94.6)	1334	(87.1)	433	(82.6)	211	(79.9)
	In last pregnancy	Yes	212	(5.4)	51	(3.3)	21	(3.6)	12	(4.5)
		No	3683	(94.6)	1481	(96.7)	563	(96.4)	252	(95.5)
MISCARRIAGE	**In any past pregnancy**	Yes	495	(12.7)	630	(41.1)	340	(64.9)	208	(78.8)
		No	3400	(87.3)	902	(58.9)	184	(35.1)	56	(21.2)
	In last pregnancy	Yes	495	(12.7)	367	(24.0)	193	(36.8)	129	(48.9)
		No	3400	(87.3)	1165	(76.0)	331	(63.2)	135	(51.1)
STILLBIRTH	**In any past pregnancy**	Yes	41	(1.1)	47	(3.1)	28	(5.3)	16	(6.1)
		No	3854	(98.9)	1485	(96.9)	496	(94.7)	248	(93.9)
	In last pregnancy	Yes	41	(1.1)	20	(1.3)	6	(1.1)	4	(1.5)
		No	3854	(98.9)	1512	(98.7)	518	(98.9)	260	(98.5)
ECTOPIC PREGNANCY	**In any past pregnancy**	Yes	27	(0.7)	34	(2.2)	19	(3.6)	9	(3.4)
		No	3868	(99.3)	1498	(97.8)	505	(96.4)	255	(96.6)
	In last pregnancy	Yes	27	(0.7)	20	(1.3)	8	(1.5)	4	(1.5)
		No	3868	(99.3)	1512	(98.7)	516	(98.5)	260	(98.5)
LOW BIRTHWEIGHT	**In any past pregnancy**	Yes	164	(4.2)	99	(6.5)	58	(11.1)	32	(12.1)
		No	3731	(95.8)	1433	(93.5)	466	(88.9)	232	(87.9)
	In last pregnancy	Yes	164	(4.2)	51	(3.3)	16	(3.1)	7	(2.7)
		No	3731	(95.8)	1481	(96.7)	508	(96.9)	257	(97.3)
PRETERM DELIVERY	**In any past pregnancy**	Yes	181	(4.6)	107	(7.0)	59	(11.3)	38	(14.4)
		No	3714	(95.4)	1425	(93.0)	465	(88.7)	226	(85.6)
	In last pregnancy	Yes	181	(4.6)	55	(3.6)	17	(3.2)	8	(3.0)
		No	3714	(95.4)	1477	(96.4)	507	(96.8)	258	(97.0)
LIVEBIRTH	**In any past pregnancy**	Yes	3115	(81.7)	1396	(91.1)	505	(96.4)	256	(97.0)
		No	700	(18.3)	136	(8.9)	19	(3.6)	8	(3.0)
	In last pregnancy	Yes	3115	(81.7)	1069	(69.8)	294	(56.1)	112	(42.4)
		No	700	(18.3)	463	(30.2)	230	(43.9)	152	(57.6)

Table 9.9: Summary table for the association between past adverse outcomes and secondary infertility defined as TTP ≥ 12 months

		Pregnancies	Time to pregnancy ≥12 months for current pregnancy			
		N	n	%	Crude OR (95% CI)	Adjusted OR (95% CI)[1]
TERMINATION						
In any past pregnancy	Yes	554	54	(9.7)	1.17 (0.83, 1.65)	1.15 (0.82, 1.63)
	No	5661	479	(8.5)	1.00	1.00
In last pregnancy	Yes	296	27	(9.1)	1.07 (0.72, 1.61)	1.09 (0.73, 1.64)
	No	5919	506	(8.5)	1.00	1.00
CLINICALLY INDICATED TERMINATIONS						
In any past pregnancy	*Yes*	*72*	*13*	*(18.1)*	***2.38 (1.12, 5.07)***	***2.31 (1.07, 4.98)***
	No	*6143*	*520*	*(8.5)*	*1.00*	*1.00*
In last pregnancy	*Yes*	*45*	*6*	*(13.3)*	*1.65 (0.69, 3.92)*	*1.62 (0.68, 3.86)*
	No	*6170*	*527*	*(8.5)*	*1.00*	*1.00*
NON-CLINICALLY INDICATED TERMINATIONS						
In any past pregnancy	*Yes*	*489*	*42*	*(8.6)*	*1.00 (0.69, 1.46)*	*0.99 (0.68, 1.44)*
	No	*5726*	*491*	*(8.6)*	*1.00*	*1.00*
In last pregnancy	*Yes*	*251*	*21*	*(8.4)*	*0.97 (0.62, 1.53)*	*1.00 (0.63, 1.57)*
	No	*5964*	*512*	*(8.6)*	*1.00*	*1.00*
MISCARRIAGE						
In any past pregnancy	Yes	1673	166	(9.9)	**1.25 (1.02, 1.53)**	1.21 (0.98, 1.49)
	No	4542	367	(8.1)	1.00	1.00
In last pregnancy	Yes	1184	117	(9.9)	1.22 (0.99, 1.51)	1.21 (0.96, 1.52)
	No	5031	416	(8.3)	1.00	1.00
1st TRIMESTER MISCARRIAGE						
In any past pregnancy	*Yes*	*1386*	*141*	*(10.2)*	***1.28 (1.03, 1.59)***	*1.24 (0.99, 1.54)*
	No	*4829*	*392*	*(8.1)*	*1.00*	*1.00*
In last pregnancy	*Yes*	*949*	*94*	*(9.9)*	*1.21 (0.95, 1.53)*	*1.19 (0.94, 1.53)*
	No	*5266*	*439*	*(8.3)*	*1.00*	*1.00*
2nd TRIMESTER MISCARRIAGE						
In any past pregnancy	*Yes*	*369*	*31*	*(8.4)*	*0.98 (0.66, 1.44)*	*0.96 (0.65, 1.42)*
	No	*5846*	*502*	*(8.6)*	*1.00*	*1.00*
In last pregnancy	*Yes*	*235*	*23*	*(9.8)*	*1.16 (0.75, 1.80)*	*1.14 (0.74, 1.78)*
	No	*5980*	*510*	*(8.5)*	*1.00*	*1.00*
STILLBIRTH						
In any past pregnancy	Yes	132	18	(13.6)	1.71 (0.90, 3.23)	1.75 (0.94, 3.37)
	No	6083	515	(8.5)	1.00	1.00
In last pregnancy	Yes	71	10	(14.1)	1.76 (0.90, 3.44)	1.74 (0.89, 3.42)
	No	6144	523	(8.5)	1.00	1.00
ECTOPIC PREGNANCY						
In any past pregnancy	Yes	89	23	(25.8)	**3.84 (2.30, 6.40)**	**3.72 (2.26, 6.14)**
	No	6126	510	(8.3)	1.00	1.00
In last pregnancy	Yes	59	15	(25.4)	**3.71 (2.04, 6.73)**	**3.65 (2.00, 6.64)**
	No	6156	518	(8.4)	1.00	1.00
LOW BIRTHWEIGHT						
In any past pregnancy	Yes	353	34	(9.6)	1.14 (0.79, 1.65)	1.13 (0.79, 1.64)
	No	5862	499	(8.5)	1.00	1.00
In last pregnancy	Yes	238	28	(11.8)	1.44 (0.96, 2.17)	1.46 (0.97, 2.19)
	No	5977	505	(8.4)	1.00	1.00
PRETERM DELIVERY						
In any past pregnancy	Yes	385	44	(11.4)	**1.41 (1.00, 1.98)**	1.39 (0.99, 1.95)
	No	5830	489	(8.4)	1.00	1.00
In last pregnancy	Yes	261	35	(13.4)	**1.70 (1.16, 2.47)**	**1.71 (1.18, 2.50)**
	No	5954	498	(8.4)	1.00	1.00

[1]Adjusted for age of woman at pregnancy and year of pregnancy
N.B. Odds ratios in bold are significant at $p<0.05$

Chapter 10: National Women's Health Study - Discussion

This chapter provides a summary of the results from the analyses of NWHS data presented in the preceding two chapters. The results are discussed in context, with reference to existing literature and in view of the strengths and limitations of the data source and analysis strategies.

10.1 OVERVIEW OF MAIN FINDINGS

The analyses conducted using NWHS data represent findings from the largest population-based survey of women's reproductive histories carried out in the UK. This work had two broad overall aims: to measure the prevalence of infertility and use of infertility treatment in the UK, and to explore the hypothesis that one or more prior adverse reproductive events has an impact on secondary infertility in women.

In both the Stage 1 and Stage 2 samples, unresolved infertility was reported by 2.5-5% of women, with the exact estimates varying according to whether pregnancy or birth was the outcome. A significant number of women reported ever experiencing infertility (including resolved infertility): averaging between 5-20% across all age groups, again varying according to the definition used and with very slight fluctuations in prevalence depending on whether Stage 1 or Stage 2 data were used. Among women aged 40-55, we observed a trend for later born women (aged 40-44) to report higher levels of infertility compared to earlier born women (aged 50 and over). This trend was apparent for all measures of infertility apart from TTP-based infertility (only measured in Stage 2). Among women in this age group who had sought help for fertility problems, later born women tended to report a slightly older age at first consultation. In all age groups there was very strong overlap between different measures of infertility.

Over one thousand (n=1036, 13.6%) of women reported undergoing medical investigations for infertility. Where both the woman and her male partner had been investigated, the most common outcome was diagnosis of female factor infertility. Of

women reporting at least one diagnosis, the most frequent was ovulatory problems. Among women reporting fertility treatment, just over half received drugs only, one quarter IVF/ICSI, and the remainder received another type of ART or non-ART treatment. Approximately one in twenty five women who had been pregnant reported at least one pregnancy conceived as a result of fertility treatment. Among women aged 40-55, more recently born women (40-44) reported a higher proportion of pregnancies conceived in this manner.

An investigation of ever experiencing reproductive outcomes of interest by infertility status revealed significant correlations between infertility and specific reproductive outcomes. These associations were strongest with self-reported infertility, where ever experiencing a miscarriage, termination or ectopic pregnancy was more frequently reported by those with self-reported infertility compared to those with no history of self-reported infertility. There were consistent patterns with regard to miscarriage and ectopic pregnancy, with women with a history of self-reported infertility, help-seeking infertility and those with TTP-based infertility all more likely to report ever experiencing these events compared to the relevant baseline groups.

In a more detailed look at relationship between prior adverse outcomes and infertility, results varied by definition of infertility, with self-reported infertility in general more strongly associated with adverse outcomes than TTP-based infertility. Adjustment for potential confounders reduced the strength of most observed associations. In adjusted analyses, self-reported infertility was significantly associated with a history of termination, first trimester miscarriage and ectopic pregnancy; although in some cases the association was only apparent when the outcome was experienced in any previous pregnancy, in other cases, where it occurred in the last pregnancy. Only a history of clinically indicated termination, ectopic pregnancy or preterm delivery was significantly associated with later TTP-based infertility. Again, to some degree these associations depended on whether the prior adverse outcome was experienced in the last or any previous pregnancy.

10.2 INFERTILITY PREVALENCE

Unresolved infertility measured either as never being pregnant (primary unresolved infertility) or never achieving a live birth despite trying, was reported by one in 40 (2.5%, Stage 2) and one in 20 (5.1%, Stage 2) women respectively. In women aged 40-55 at the time of the survey, the prevalence varied between 2.3-2.4% and 3.6-4.3% respectively, depending on whether the estimate was taken from Stage 1 or Stage 2 data. These results are largely consistent with a number of different studies carried out in the UK over the last two decades which report a prevalence of primary unresolved infertility (no pregnancies) of between 2.2-4.0%[3-6, 8] and unresolved infertility with no births between 2.8-4.7%.[6, 8] In the data reported here, there was a slight trend of decreasing prevalence with increased age once women aged 40-55 were stratified into five year age groups. These findings are in contrast to a comparison of results from two studies carried out Aberdeen, one in 1988 and the second in 2007, which provide no evidence of a rise in unresolved infertility among women aged 46-50 years.[3-4]

One in five women reported experiencing problems trying to conceive at some point in their life. Other UK studies have not used this exact self-defined measure of infertility, but instead have qualified this definition by the time period that women have spent unsuccessfully trying to conceive. Therefore the nearest equivalent infertility measure is infertility experienced for a period of 12 or 24 months. Other UK population-based studies have reported a prevalence of 12 month infertility of 17% [3, 8] and 26%, [6] and 24 month infertility as 9%,[3] 12%,[8] 13%,[6] and 14%.[4-5] In our results, women aged 40-55 from the most recent birth cohort (aged 40-44) had slightly higher prevalence estimates compared to earlier born women, although this trend was not significant. Two other studies compared time-based definitions of infertility across age groups and failed to observe a difference in prevalence by age.[3, 6] However, the results of one of these studies,[3] when compared to a similar survey conducted in the same geographical area nearly twenty years before, suggests that a history of infertility of 24 months or longer decreased among women aged 46-50 during this time period.[4]

Sixteen percent of women in the NWHS sample had sought medical help for fertility problems. This figure represents approximately 82% of the women who reported problems getting pregnant. Estimates from other studies of the proportion of women or

couples with problems who seek medical help range widely, with UK studies reporting estimates ranging from 48-95%.[3-8] One recent review of both UK and non-UK studies suggests that on average of 56% of those with problems conceiving seek medical help.[31] Comparing the results reported in Chapter 8 to prevalence estimates from these other studies suggests the prevalence of help-seeking in the NWHS sample was higher than expected.

Slightly lower proportions of women in the youngest and oldest age groups reported seeking medical help. Again, a trend similar to those observed earlier was identified, with the youngest women (40-44) in the older age group (40-55) more likely than the oldest women (50-55) to have ever sought help (17.5% vs. 14.5%). Both Aberdeen studies reported similar findings when comparing women aged 36-40 to those aged 46-50, with higher proportions of women aged 36-40 having sought help.[3-5] In another UK survey of women aged 36-50, compared to older women younger women were more likely to both consult their GP and to be referred for specialist help at hospital.[6]

Another trend we observed regarding help-seeking behaviour was that among women aged 40-55 who sought medical help, more recent birth cohorts tended to consult first at a slighter later age. To our knowledge these findings are unique with this phenomenon not previously reported in other population-based studies. This was a key finding of the analysis of Stage 1 data, published in the journal *Human Reproduction.*[73] One very recent clinic-based study conducted in the Netherlands reported an increase in the average age of patients presenting for fertility advice and treatment between 1985-2008.[362] This is consistent with established trends of increasing age at first childbearing – if later-born women 'test' their fertility at an increasingly older age, it is to be expected that the average age at first consultation for fertility problems will increase accordingly. This shift in the demographics of the subfertile population has important implications for future service demand and delivery.

Eight percent of all women reported ever receiving fertility treatment. In the literature review described in Chapter 3, we identified no UK studies which reported on the prevalence of use of treatment in this way. Again, among women aged 40-55, younger women (40-44) were more likely to have received fertility treatment than earlier born

women (50-55). Although this data is not supported by evidence from other studies, it is an unsurprising finding and likely to reflect growing availability and acceptability of fertility treatment.

Of women who had been pregnant, 16% indicated that they had at least one TTP of 12 months or more. This prevalence (16%) is identical to the average proportion of pregnancies reported as taking 12 months or more to conceive in a series of surveys carried out in European countries.[363] Although more women aged 35 and over reported having experienced a conception delay of this kind, there was no discernable trend by age group in women over this age. Therefore, this does not support the overall trends reported in earlier sections for the youngest age group among women aged 40-55 to report higher levels of both observed and proxy measures of infertility compared to the oldest age group.

One unique feature of the analyses reported in this thesis was the ability to look at multiple definitions of infertility. Across the whole sample, the highest prevalence of infertility resulted from self-reported infertility (20%), similar numbers were observed as infertile according both the consulting and TTP measure (16% for both), and the lowest prevalence found with ever receiving fertility treatment (8%). When restricted to women who had been pregnant and reported at least one TTP (to ensure equivalence of denominators across all definitions), there was a clear trend with age, with women aged 35-39 reporting the highest levels of infertility according to all four definitions. Looking only at women defined as infertile according to at least one definition, there was significant overlap between definitions with half of women defined as infertile according to all three measures. This represents one of the truly unique findings of the investigations reported here, as overlap between definitions has not been reported in any other published study. Studies carried out in Australia, USA and Tanzania have measured infertility using a number of different methods in the same population.[25, 56-57] These studies all reported different estimates of prevalence according to differing definitions, but none evaluated the overlap between definitions.

Our results confirm that a significant proportion of women experience infertility. However, the overall proportion of those with unresolved infertility is low, and the vast

majority of women who seek medical help for infertility end up conceiving and achieving a live birth. Different approaches to measuring infertility provided different estimates of prevalence. Ideally, prevalence studies should explore the use of multiple indicators of infertility, alongside a careful consideration of the strengths and limitations of each. For example self-reported infertility, although a crude measure which is difficult to validate, is nonetheless important because it is not restricted to those who eventually conceive. The need to clarify and define infertility measures used in prevalence estimates cannot be understated.

Where suitable comparison studies exist, the prevalence estimates calculated from NWHS data are broadly consistent with results from other UK studies. In general, a slightly higher prevalence of infertility was frequently observed in the youngest age groups. This suggests that among younger respondents, those who experienced problems may be disproportionately represented. A key finding was that when prevalence measures were reported separately for women aged 40-55, a dose-response association was observed between age and infertility.

In the descriptive analyses discussed above, infertility appeared to be correlated with other adverse reproductive outcomes, though association varied according to definitions used. These associations were further explored in more detail in Chapter 9, the results of which are discussed in the following section.

10.3 INFERTILITY INVESTIGATIONS AND TREATMENT

Of the women who reported having investigations for fertility problems, in the vast majority of cases (83%) both the male and female partner had been investigated. This 83% of cases could be subdivided into those cases that these resulted in a female factor diagnosis (approximately one third overall), those in which male factor infertility was diagnosed (13%), those in which problems were found in both partners (16%), and the one in five investigations that resulted in a diagnosis of 'unexplained infertility'. Of female diagnoses, ovulatory problems were the most common diagnosis, followed by tubal problems and endometriosis. It is difficult to compare consistency across different studies due to the variety of ways in which diagnoses are categorised and reported across male and female partners. However, in a 1997 survey, Buckett and Bentick

reported that more than half (54%) of responders indicated that a female cause of infertility had been diagnosed, and in 29% of 14% of cases unexplained infertility and male factor infertility was respectively diagnosed.[8] The most recent UK study data collected in 2007 by Bhattacharya and colleagues reported that in approximately 23-32% of cases infertility was diagnosed as due to ovulatory problems, tubal problems were attributed to 12-14%, endometriosis to 10-11%, other problems were diagnosed in 14-21% of cases, and 24-29% and 29-30% were attributed to male factor infertility and unexplained infertility respectively.[3] The slight variations in the figures reported is due to diagnoses being reported according to whether the infertility was primary or secondary. National UK clinic data reports that of patients undergoing IVF in 2008, 30% had been diagnosed with male factor infertility, 28% with female factor infertility, and 10% had been diagnosed with both.[364]

Eight percent of women reported that they and/or their male partner had received fertility treatment at some point. Over half of these women reported that they had received drug treatment only, one quarter had received IVF/ICSI, and the remainder had either received other ART only or other non-ART treatment. The lack of research data makes it difficult to compare these results to findings from other studies.

Of women who had been pregnant, approximately one in 20 (4%) reported at least one pregnancy resulting from fertility treatment. Less than a quarter reported two or more pregnancies conceived in this way. In the 40-55 year old age group there was a trend by birth cohort, with more recently born women (aged 40-44) reporting a higher proportion of pregnancies conceived in this way. Again, there is little published information on the proportion of women who conceive as a result of fertility treatment. In recent years, the UK regulatory body the Human Fertilisation and Embryology Authority (HFEA) has required registered clinics to submit data, and this has been used to try and estimate the proportion of births attributable to ART in the UK,[364] However, this is not easily compared to the results presented here due to the different denominator (births rather than women or pregnancies). Furthermore, HFEA data does not distinguish between births and conceptions occurring in women resident in the UK and those from other countries who receive treatment in the UK. Additionally, there is no statutory requirement to report data on women receiving ovarian stimulation, so HFEA data

relates only to women undergoing ART or donor insemination. Two UK surveys have attempted to estimate the proportion of UK births attributable to fertility treatment.[365-366] In a survey of all births occurring in UK maternity units in one week in 2003, Bardis and colleagues reported that 1.9% were conceived with assistance (defined as ovulation induction, AI, assisted conception technologies).[365] In data from the Millennium Cohort Study (MCS), a nationally representative survey of infants born between 2000-2001, 2.5% of mothers reported that infertility treatment had led to the conception of the relevant infant. This survey used the slightly broader definition of infertility treatment, which included pharmacological treatment, assisted reproductive technologies, and surgical treatment unrelated to egg retrieval or embryo transfer.[366] It is difficult to compare these two figures (1.9% and 2.5%) to the figure reported in NWHS analyses (4%), primarily because the two are different measures. The NWHS figure is a woman-based measure reporting the number of women who conceived at least one pregnancy as a result of fertility treatment. The figure reported by Bardis and colleagues and the MCS data is a proportion of births – and indeed, in the MCS study, this information was based only on infants who survived to at least 9 months of age.

10.4 REPRODUCTIVE OUTCOMES BY INFERTILITY STATUS

Crude standardised event ratios (SERs) suggested that certain reproductive outcomes were more commonly experienced by women who reported infertility. SERs were calculated separately for the three main indicators of infertility: self-reported infertility, treatment-seeking infertility, and TTP-based infertility. Women with self-reported infertility were less likely to report ever having a stillbirth, but more likely to report ever having a miscarriage, termination and ectopic pregnancy. Compared to women who had not ever sought help for fertility problems, help-seekers were less likely to report ever having a livebirth, and more likely to report both having a miscarriage and ectopic pregnancy. Using the TTP-based indicator of infertility (limited to those who had been pregnant and had reported at least one TTP), women with infertility were more likely to ever report experiencing miscarriage and ectopic pregnancy. The results were descriptive only and did not adjust for potential confounders apart from age. Nevertheless, they are consistent with previous literature which generally supports an association between infertility (defined in various ways) and both miscarriage and ectopic pregnancy.[3, 297, 299, 303-304, 309, 313, 367]

Of women who received fertility treatment, the vast majority went on to conceive a pregnancy (93%) and live birth (92%). These figures do not necessarily represent those conceptions attributable to treatment, as some of these pregnancies are likely to have been conceived spontaneously. In general, these results suggest good future outcomes for women who report infertility. In an earlier study in Aberdeen, among women who sought medical help, 58% of women who reported primary infertility and 67% of women who reported secondary infertility went on to conceive a pregnancy.[3] It may be that those who sought and received treatment in the NWHS sample were a specific sub-sample with characteristics associated with a higher chance of success.

We found that probability of both pregnancy and birth were associated with age, with women who sought help at a younger age more likely to subsequently experience both a pregnancy and live birth. This finding is expected and reflects overall higher rates of fertility among younger age groups.

10.5 SECONDARY INFERTILITY AND PRIOR ADVERSE REPRODUCTIVE OUTCOMES

The analysis which concentrated on the effect of prior adverse events on risk of secondary infertility, by necessity involved examination of secondary infertility. Nearly five percent of pregnancy attempts were characterised by self-reported secondary infertility. This proportion varied with age, calendar time, and pregnancy attempt order, with the highest proportion of self-reported secondary infertility observed among women older at the time of pregnancy attempt, recent time periods, and second pregnancy attempts. The finding that self-reported secondary infertility was associated with age was unsurprising and confirms the established association between age and female fertility.[99] This measure of infertility was more commonly reported in recent pregnancy attempts, providing further evidence to the equivocal discussions of whether infertility is on the rise.

In fully adjusted analyses, a history of the following adverse outcomes was associated with an increased likelihood of self-reported infertility in the index pregnancy attempt: termination, clinically indicated termination (in any past pregnancy), non-clinically

indicated termination, miscarriage (last pregnancy only), first trimester miscarriage (last pregnancy only), and ectopic pregnancy. There was no consistent evidence that second trimester miscarriage, stillbirth, low birthweight or preterm delivery were associated with self-reported infertility in the index pregnancy.

Of the index pregnancies included in this analysis, 16% had a TTP of 12 months or more. TTP was strongly correlated with use of fertility treatment, with pregnancies conceived in this manner much more frequently reported as taking 12 months or more to conceive. The fact that TTP was strongly correlated with use of treatment is intuitive and expected. There was no consistent evidence to support an association between TTP in the index pregnancy and any of the following factors: age at pregnancy, year of pregnancy, and number of previous pregnancies.

Evidence to support an association between past adverse outcome and TTP-based secondary infertility was in general weak. In fully adjusted analyses, only a history of clinically indicated termination in any past pregnancy, ectopic pregnancy in either the last or any previous pregnancy, and preterm delivery in the last pregnancy, were associated with TTP-based secondary infertility in the index pregnancy.

It might be expected that the latter two adjusted analyses would show similar results. However, this would only be the case if both self-reported infertility and TTP-based infertility measure similar outcomes. According to results reported in Chapter 8, 15% of women who were classified as infertile according to at least one measure of infertility reported self-reported infertility without TTP-based infertility. The two samples differ, and crucially, the TTP-based infertility does not include women who attempted to conceive but failed to do so (unresolved infertility).

As described in Chapter 3, the epidemiological literature investigating the association between prior adverse outcomes and infertility is minimal. More commonly the focus has been the reporting of such outcomes as ever experienced, without consideration of timing. There is however a growing body of literature which has also investigated the association between infertility and future reproductive outcomes.

We found inconsistent evidence of an association between termination and infertility. The weight of existing literature mostly does not support the hypothesis that termination has a adverse effect on future fertility. [297-302, 368-370] Therefore, our finding that in some cases termination was associated with subsequent infertility is contrary to much of the existing literature. However, the majority of studies which have investigated this association have not taken into consideration additional explanatory factors, such as the indication for termination, the method used, or the timing of the termination. In the present work, trends suggested that clinically indicated terminations may be more likely to be associated with subsequent infertility than non-clinically indicated terminations. In the UK, terminations carried out for medical reasons[1] are on average carried out a later gestation than other terminations, particularly those that are carried out for reasons of fetal abnormality, as these are usually only detected during routine screening which takes place between 11-20 weeks. Current guidelines suggest that terminations at or beyond 15 weeks should be carried out using dilation and evacuation. Induced terminations carried out in the second trimester carry a significantly higher risk of morbidity compared to those carried out early in pregnancy.[371-372] In addition, the exploration of the relationship between termination and infertility is complicated further when more subjective measures of infertility are used – as in the self-reported measure of infertility used in the analyses reported here. It is possible that women who have undergone a termination in the past are quicker to define any delay in conceiving as problematic. Ascertaining the true relationship between prior termination and fertility is further complicated by the fact that highly fertile women may be over-represented in those seeking termination. This may help to explain some of the surprising results in a number of studies, where termination appears to be a protective factor.[296, 368, 373]

Most studies that have investigated the effect of prior miscarriage on subsequent infertility have reported an association,[297, 303, 373-374] although these findings are not universal.[299] We only observed an association where infertility was defined as self-reported infertility rather than delayed conception. Additionally, this association was

[1] Medical terminations are defined here as those carried out for the following reasons:

- Continuation of pregnancy would involve risk to the life of the pregnant woman
- Termination may prevent grave permanent injury to the physical or mental health of the pregnant women
- The presence of fetal abnormalities

only observed where the miscarriage occurred in the last pregnancy, and once we stratified by timing of miscarriage, only first trimester miscarriage was shown to be associated. The fact that first trimester miscarriage showed a stronger relationship with infertility is biologically plausible. There is a degree of overlap between early fetal loss and infertility, particularly where fetal loss occurs at subclinical stages and is therefore classified instead as problems conceiving, or infertility. Again, the subjective nature of this measure of infertility may be important – with women who have a history of miscarriage quicker to perceive themselves as subfertile.

The strongest and most consistently observed association was between ectopic pregnancy and infertility. This finding was observed in both the analysis using self-reported infertility, and the analysis using TTP-based infertility. Ectopic pregnancy is a well established risk factor for infertility, supported both by a strong body of evidence[299, 367, 374] and a well understood biological mechanism.

Preterm delivery in the last pregnancy was associated with TTP-based infertility in the index pregnancy. We were unable to identify any other studies which consider the risk of infertility according to history of preterm delivery, although a number of studies have investigated the association between preterm delivery and infertility across a woman's reproductive career. The results of these studies are mixed, with some studies reporting that women with a history of infertility are also more likely to report preterm birth,[313-314] although other studies have reported no significant associations.[315-316]

10.6 STRENGTHS AND LIMITATIONS

The size and population-based nature of the NWHS are significant strengths of this study; representing the largest population-based survey of women's reproductive histories carried out in the UK. This study allowed a unique investigation of factors associated with reproductive outcomes in UK women. In particular, a substantial degree of information was collected on fertility problems experienced by the women; information which is not routinely available from any other source.

Response rates, bias and representativeness

NWHS was a population-based survey, designed to be representative of the target population of UK adult women aged under 55. The response rate for Stage 2 of the NWHS was 73%, but taking into account the response rate for Stage 1, which was 46%, the overall response rate was considerably lower. Low response rates are a common issue with postal surveys, and the overall response rate (taking Stage 1 into account) was lower than the one observed in a more recent survey carried out by Bhattacharya and colleagues, who had a 50% response rate.[3] Other postal surveys carried out in the 1990s reported higher response rates.[4-5, 8]

In order to assess the importance of low response rates in epidemiological surveys, it is necessary to consider is whether response is biased – that is, whether those that respond systematically differ from those who do not.

To investigate the likelihood of biased response, comparisons were made of responders and the general UK female population according to a number of specific indicators. This exercise was conducted for Stage 1 responders and is reported in the methodology paper referenced earlier, a copy of which is provided in Appendix 3.[356] In brief, a formal statistical comparison revealed that registered stillbirths and multiple deliveries occurred in NWHS women in similar rates to women in the general population.[356] Maternal age at first pregnancy was also compared between NHWS women and the general population and found to be similar, although no statistical comparisons were provided as national data was only available for births occurring within marriage and the NHWS questionnaire did not collect information on marital status at the time of birth.[356] Whether or not conclusions about the representativeness of Stage 1 can be generalised to Stage 2 depend on differences between the Stage 1 and Stage 2 samples. The data presented early in Chapter 8 suggests that the Stage 2 sample used in the present work was representative of Stage 1 responders according to the wide range of sociodemographic and reproductive variables considered.

Although the NWHS sample has shown to be representative of the target population in terms of the rate of stillbirths and multiple deliveries, and likely to be representative in terms of maternal age, it is still possible that response was associated with the outcome

under study in this thesis: infertility. It is possible that women who had experienced problems with fertility were less likely to respond to the survey. Our ability to compare responders to the general UK female population in terms of the measures investigated in this thesis (infertility prevalence, use of fertility treatment etc.) are hampered by the paucity of high quality data collected either routinely or by other research studies. It is however worth noting that the percentage of liveborn infants resulting from ART between 1997-2001 is very similar to the overall figure reported for the UK 1997-2001 by the European Society of Human Reproduction and Embryology (ESHRE). A comparison of these data are presented in Table 10.1. This of course is only a measure of resolved infertility. Those women who suffered fertility problems and never conceived, or conceived but never delivered a live birth, would not be represented in these figures. Nevertheless, estimates of infertility prevalence calculated in the present work were largely consistent with the findings of the few other UK population-based surveys, particularly in terms of unresolved infertility. The exception to this was estimates of help-seeking for fertility problems and the proportion of women conceiving and giving birth after fertility treatment, all of which appeared higher in the NWHS sample compared to other studies. It may be that women with fertility problems who responded to NWHS were more proactive about seeking help and pursuing treatment to the point of success compared to those women with fertility problems who did not respond. This may have resulted in overestimates of both help-seeking among the infertile population and the probability of positive outcomes after fertility problems.

One final issue to consider regarding representativeness is socioeconomic status of responders. It is possible that the women that responded to NWHS are of higher socioeconomic status than women of similar age in the general population. Although there were some indicators of socioeconomic class available in the dataset, each had their limitations. For example, occupational and household income data were collected for a case-control series (where cases = miscarriage, controls = livebirths), but these data were not available for those who did not conceive. It is thus possible, and perhaps even likely, that the study population was not representative in terms of socioeconomic status.

Self-report and recall of data

All the measures of infertility used were based on self-report data. The data were not validated using other data sources and in some cases relied on self-recall of events happening a considerable time ago. The limitations of such an approach to collecting data has been widely discussed, although a weight of evidence supports the reliability and validity of women's self-report information on reproductive outcomes, even where such events occurred decades ago.[375-378]

Approaches to defining infertility

An extensive discussion of different approaches to defining and measuring infertility was provided in Chapter 3. It is clear from this review that all methods of measuring infertility have different strengths and limitations. The NWHS questionnaire collected information on a variety of different indicators of infertility, and therefore we were able to make use of a multiplicity of definitions. Descriptive analyses compared and contrasted different definitions, and for the main analysis investigating prior reproductive outcomes and secondary infertility we were able to repeat the analyses using two different measures of infertility.

It is however worth reiterating some of the key issues that arise in considering different definitions of infertility, particularly the 'threshold' for defining infertility, and the use of TTP-based measures of infertility. For the measure of self-reported infertility, we relied on women to self-define infertility. We did not qualify this definition as some other studies have done – where for example 'problems conceiving' may be defined as engaging in regular unprotected sexual intercourse for a period of 12 months or more without conceiving. Leaving it to women to define infertility themselves in this way has both advantages and disadvantages. It can be considered a useful measure of infertility, as it possibly the one most relevant to quantifying the burden of infertility in terms of service provision. The point at which women define themselves as experiencing problems conceiving is likely to be their own trigger point for seeking help. However, the decision to self-define as having problems may be influenced by a number of factors including accessibility to medical help, anxiety resulting from previous experience, and the degree to which a pregnancy is actively sought.

As discussed in some detail in Chapter 3, TTP is a commonly used epidemiological indicator of infertility, but has some important limitations. Most obviously, this measure of infertility can only be calculated for women who actually conceive a pregnancy, therefore, unresolved infertility and sterility cannot be captured using this definition. Retrospective studies such as NWHS rely on retrospective recall of TTP and it has been suggested that this may result in bias. However, numerous studies provide evidence that TTP can be reliably recalled over a lengthy retrospective period.[18-20] A number of other limitations are associated with TTP studies. These include the propensity for 'wantedness bias' (the tendency for unintended pregnancies to be later defined as intended, increasing the proportion of 'quick conceivers'), and the fact that women experiencing unintended pregnancies tend to have higher than average fertility (therefore, the exclusion of such pregnancies has the reverse effect, reducing the proportion of couples with high fertility). This dilution of the sample may go some way to explaining why associations between prior adverse outcomes and subsequent infertility that we observed were weaker when TTP-based infertility was the outcome. Right truncation was considered to have particular implications for the TTP-based analysis of infertility, with 'quick conceivers' over-represented in the most recent conceptions. For this reason, we excluded from the main analyses all pregnancies that were estimated to begin in the two years preceding the survey. In addition, the NWHS questionnaire only collected data on TTP in grouped categories rather than as a linear variable, with the final category defined as '12 months or more'. Therefore, we had no information on the exact length of TTP among those with delayed conception. This is unlikely to be an important limitation, as some authors recommend that TTP is censored at 12 months anyway due to this commonly being used as threshold at which point to seek fertility treatment. Lastly, it can sometimes be difficult disentangling recurrent early fetal loss and the use of fertility treatment from TTP measures. The former issue was addressed by a careful examination of the data, resetting the TTP interval where it was found that women had included pregnancies ending in miscarriage in their own calculation of TTP for the index pregnancy. To check the effect of infertility treatment on reported TTPs, the final models for TTP-based infertility were re-run excluding pregnancies resulting from infertility treatment. Overall, these confirmed the general patterns observed in the analysis including all pregnancies.

We also considered medical help-seeking for fertility problems as a proxy for infertility, although we did not use this definition in the main adjusted analyses. The key issue with this definition is that help-seeking behaviour is likely to be influenced by a number of factors, and therefore this measure reflects not only fertility problems but the propensity to seek medical help. Those that seek help are in general a highly self-selected sample. This issue goes some way to explain the wide ranging estimates of help-seeking behaviour ascertained from different studies. Despite this, the high estimates of help-seeking reported in the NWHS sample suggest less variation in help-seeking behaviour in this sample.

Validity of subgroup analyses

We sampled women under 55 across a wide age range, and did not restrict inclusion to women who had completed their fertility. Therefore, there is an issue of right truncation to consider: many women who responded to the survey may still have been in the process of completing their fertility. For this reason, some descriptive analysis was restricted to the 'older' women in the sample (aged over 40). This is in line with the suggestion that resolved infertility is best investigated only in women who have completed their fertility. Results were often reported separately for the 40-55 year old age group. However, some of these women may not yet have completed their fertility. Delayed childbearing means that increasingly women are having children later in life.[379] It is possible that higher infertility in the youngest 'old' age groups (40-44) may be an artefact, with lifetime prevalence not accurately estimated in this age group as some women may have infertility that will be resolved. It has been previously noted that restricting samples to women who have completed their fertility may be a poor indication of service need.[3] For this reason, estimates for the whole cohort of women were presented alongside subgroup estimates in the vast majority of cases,

The role of male factor infertility

Although the NWHS survey collected information on male factor infertility, the data were limited. The focus in reported analyses was on infertility as observed in women, and the relationship between this and other reproductive events. Nevertheless, it is an important limitation of these analyses that male factor infertility was not taken into account, and there was no way to isolate whether reported infertility was attributable to

the female partner, male partner, or both. This would have the effect of reducing the ability of the analyses to detect any real association, should it exist.

Study power

Despite the low response rate for Stage 2 of the NWHS survey, the participating sample was still large with 7700 women reporting over 18,000 pregnancies and pregnancy attempts. Descriptive analyses used the full sample, or a slightly restricted sample, and have acceptable levels of study power. However, the analyses looking at the effect of past reproductive history and secondary infertility were conducted using much smaller samples, although the analysis of past miscarriage and self-reported infertility did meet the minimum sample size requirements discussed in 7.2.5. This was in part due to the low proportion of women in the sample who experienced secondary infertility, and also due to specific inclusion criteria applied to ensure the correct denominator was used in statistical analyses. For self-reported infertility, nearly 9000 pregnancy attempts were included, with the remaining attempts excluded for any of the following reasons: they were first pregnancy attempts, women had not indicated whether they had ever experienced problems getting pregnant, pregnancy attempt occurred after the first episode of infertility. The analysis using TTP-based infertility was conducted using an even smaller sample of 6200 pregnancies, with remaining pregnancies excluded either because they represented first pregnancies, because of restrictions due to truncation bias, or because the pregnancy was unplanned or no TTP was reported. For those relationships were no association was found (for example, in some of the analyses looking at the effect of prior miscarriage), a larger sample size (greater study power) may have increased the chance of detecting an association, should one exist. This would be equivalent to reducing the probability of a type II error.

Confounding

In general, the descriptive analyses reported here did not adjust for confounding, with the exception of standardised event ratios which controlled for age. In the adjusted analyses looking at fertility rates and prior reproductive outcomes, we attempted to adjust for relevant confounders. However, we found little evidence of confounding and therefore only included important *a priori* confounders in the final adjusted models. With any epidemiological study there is always the issue of unmeasured confounding.

Accurate information on several important variables including occupation/socioeconomic status and smoking (ideally all measured at multiple time points) were not available in the NWHS dataset. It is possible that these factors may have helped to further clarify the relationships investigated in the reported analyses.

10.7 CONCLUSIONS

The results reported here represent findings from a large population-based survey of women's reproductive histories. They provide a descriptive epidemiology of infertility in the UK, comparing and contrasting multiple indicators of infertility. These descriptive results provide an important contribution to the existing literature, particularly with regard to patterns in women more likely to have completed their fertility. They present rarely reported data on the use of ART and other fertility treatment. Multivariate analyses of the data were conducted to investigate the relationship between prior adverse reproductive outcomes and infertility. These results provide some evidence that secondary infertility is associated with prior adverse reproductive outcomes, specifically a history of miscarriage, termination, ectopic pregnancy and preterm delivery. These associations were not consistently observed across different definitions of infertility.

NWHS was a large well-designed study, and comparisons with national and other data suggest the sample was representative. The response rate was not optimal, a limitation observed with many other postal surveys. The use of multiple indicators of infertility was a strength of the analysis, as was the detailed information available on reproductive histories.

The descriptive results seem to be consistent with existing literature, although it should be noted that the data on the epidemiology of infertility in the UK is generally lacking and it was not always possible to find suitable comparisons. In the multivariate analysis, termination was found to be associated with subsequent infertility, an association which has not often been found in previous studies. The relationship between both miscarriage and ectopic pregnancy and subsequent infertility is supported by the existing literature, particularly in the case of ectopic pregnancy, which is known to be strongly associated

with future fertility problems. Little existing literature addresses the relationship between past preterm delivery and subsequent infertility.

These results provide a unique contribution to the existing knowledge concerning both the epidemiology of infertility and the relationship between adverse reproductive outcomes and subsequent infertility.

Table 10.1. Prevalence of births attributable to ART: a comparison of NWHS Stage 2 and UK national data [380-385]

	National data			NWHS data			
	Births	Conceived by ART[1]		Births	Conceived by ART[2]		
	N	n	Prevalence %	N	n	Prevalence %	(95% CI)
1997	725,810	7,525	1.0	602	13	2.2	(1.0, 3.3)
1998	717,081	8,140	1.1	641	11	1.7	(0.7, 2.7)
1999[3]				626	4	0.6	(0.0, 1.3)
2000	679,029	7,677	1.1	633	12	1.9	(0.8, 3.0)
2001	669,123	8,933	1.3	593	11	1.9	(0.8, 2.9)
Total	2,791,043	32,275	1.2	3095	51	1.6	(1.2, 2.1)

[1]Defined as IVF, ICSI, FER or OD
[2]Defined as IVF, ICSI, GIFT, AI, or IUI
[3]1999 UK data missing

Chapter 11: Conclusions and recommendations

11.1 SUMMARY OF KEY FINDINGS

This thesis presents a critical literature review of the definition and determinants of infertility alongside the results of analyses of prevalence and risk factors for infertility in women. A brief summary of the findings of the main analyses are detailed in the following sub-sections

11.1.1 Literature review

Chapter 3 of this thesis contains an overview of the epidemiology of infertility. The first key element of this chapter was a critical evaluation of different definitions of epidemiology. From the review presented, it is clear that the existing literature is littered with inconsistent use of terms and as of yet, no satisfactory solution to the crisis in terminology has been adopted. An overview of current prevalence and trends followed, in which the difficulty in estimating prevalence was discussed with particular regard to social trends such as delayed childbearing, and the methodological limitations of existing prevalence studies. Although the idea that infertility is on the rise is a popular view, the epidemiological evidence to support such a trend appears lacking. Finally, this chapter included an extensive review of the literature regarding the determinants of infertility. A key focus was evidence regarding the role of early life and reproductive risk factors. The review suggested that there are little existing data which considers the role of early life factors and fertility. In terms of reproductive risk factors, there appears to be some existing evidence supporting the clustering of adverse reproductive outcomes.

11.1.2 Early life factors and infertility (UBCoS)

The analyses reported and discussed in Chapters 4-6 use data from a retrospective cohort study based on women born in Uppsala, Sweden, between 1915-1929. This dataset was used to investigate the possible association between early life factors, specifically markers of *in utero* growth, and fertility in adulthood. Two different indicators of fertility were used: age-specific fertility rates, and time to first live birth.

The reported analyses do not provide any evidence to support the hypothesis that markers of *in utero* growth (birthweight, gestation, birthweight for gestational age, and ponderal index) are associated with fertility in adult women. Despite the strengths of this analysis – particularly in terms of the size and quality of the data – several limitations, particularly in terms of the validity of the measure of time to first live birth, may have resulted in a reduced ability to detect any true association. Therefore, a real association between early life growth and fertility in adult women cannot be ruled out, particularly as there appears to be a small but growing literature to support a possible link.

11.1.3 Epidemiology of infertility, and prior reproductive outcomes and secondary infertility (NWHS)

The analyses reported and discussed in Chapters 7-10 are based on data from the National Women's Health Study, a population-based survey carried out in 2001 which collated the reproductive histories of over 7000 women in the UK. The first phase of investigation (reported in Chapter 8) aimed to describe the epidemiology of infertility in the UK, and provide rarely reported data on the prevalence of infertility, help-seeking for fertility problems, and the use of fertility treatment. Overall, 20% of women reported difficulties conceiving at some point in their lives, although only 4.3% women reported unresolved infertility at the end of their reproductive lives. The second phase of this work (reported in Chapter 9) looked at the relationship between prior adverse reproductive outcomes and secondary infertility. The results provide some evidence that secondary infertility is associated with prior adverse outcomes. However, although a number of associations were statistically significant in multivariate analysis, associations were not strong and not always consistently observed. NWHS has many strengths, comparisons suggest the sample was representative, and the range of fertility indicators available in the dataset represented an important feature of the reported analyses. However, as always, study limitations need to be taken into account and these are discussed in detail in Chapter 10.

11.2 RECOMMENDATIONS FOR FUTURE RESEARCH

11.2.1 Recommendations regarding data sources

Infertility is known to be a particularly difficult area to research. National and/or routinely collected data are generally of little use, as relevant surveillance data are not collected systematically. Although the first set of analyses reported in this thesis made use of routine data, this approach would not be appropriate in contemporary populations where the use of proxy indicators of fertility is unsuitable. However, it may be that other related measures, such as patterns of help-seeking behaviour and information on the receipt of fertility treatment, could be ascertained from routine data sources. The validity of such approaches would depend on the reliability and quality of available data. The alternative to routinely collected data are purposively collected data. Large population surveys, the most frequently used study design, tend to be expensive and funding is difficult to obtain. In addition, there are the usual limitations in terms of response and the difficulty in ensuring such studies are representative. The experience of NWHS and other similar population-based studies, suggest such an approach is feasible and can provide extremely useful data.

Recommendations

On the basis of the work conducted for this thesis, the need for high quality research data that can be utilised for further research work is clear. In particular, the following recommendations are made:

- Improved data collection for existing sources of routine data, for example routinely collected data on the use of regulated fertility treatments
- Innovative approaches to using existing data, for example using clinical or prescribing data such as the General Practice Research Database (GPRD)
- Linkage of existing databases (as in the Swedish experience of UBCoS Multigen); of particular use for looking at early life factors
- Consideration of a national population survey of reproductive health (similar to NWHS) to be conducted at specified time intervals; ideal for monitoring changes in prevalence
- Priority should be given to datasets which enable the comparison of multiple indicators of infertility

11.2.2 Recommendations regarding definitions and methodological approaches

The literature reviewed in Chapter 3 highlights the confusion and inconsistency surrounding the definition of infertility. At best, this impacts on the ability to draw comparisons between different studies. At worst, the lack of clarification in certain studies makes interpreting findings difficult and estimates unreliable. The need to clarify definitions used in future research cannot be overstated.

Recommendations

Researchers conducting studies on infertility need to be clear about definitions used. In addition:

- A greater acknowledgement needs to be given to the limitations inherent in many methodological approaches to studying infertility, for example those affecting TTP studies, and the 'treatment effect' in prevalence studies
- It would be useful to explore novel approaches to investigate risk factors for infertility, for example the current duration method

11.2.3 Recommendations regarding key areas of research

Chapter 3 of this thesis included a descriptive review of the current literature on risk factors for infertility. This review confirms that despite considerable research on risk factors, many research findings are still equivocal. However, a particular absence of research on the risk factors most relevant to this thesis was noted – early life factors and reproductive determinants.

Recommendations

In light of existing research and the data analysed in this thesis, it is no surprise that three particular areas are presented as worthy of future research. Further research would enable the results presented in this thesis to be synthesised along with findings from other studies, and will help to build the knowledge base relating to these particular determinants. Research in the following areas is likely to provide valuable insight into the trends, aetiology, and potential for prevention, of infertility:

- Trends in prevalence within populations over time

- Early life factors and their relationship with fertility in adulthood, particularly in women
- Clustering of multiple adverse reproductive outcomes as they occur across a woman's reproductive lifetime

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APPENDICES

APPENDIX 1 UBCoS Supplementary information

This appendix contains the following information:

- UBCoS Multigen Study information sheet
- UBCoS supplementary tables and figures

A.1.1 UBCOS MULTIGEN STUDY INFORMATION SHEET

The Uppsala Birth Cohort Multigeneration Study (UBCoS Multigen)

Introduction

Health inequalities and social determinants of health are a cause of much concern in all societies today. The Uppsala Birth Cohort Multigeneration Study is a database that recently was established at the Centre for Health Equity Studies and it offers a unique opportunity to explore several issues highly relevant for health equity research. The uniqueness of our study is mainly in the possibility to apply a life-course approach to analysis in a cohort with detailed biological and social data stretching from birth to old age, and in being able to extend the transgenerational perspective to more than two successive generations.

Aims

Our main research objectives are to:

(i) Address questions of the extent to which and the mechanisms whereby social advantage and disadvantage are transmitted from one generation to the next, giving rise to continuity in social disadvantage both over the life cycle and across generations.

(ii) Explore how early social and biological factors, especially those related to cardiovascular risk, are transmitted from the parent generation to offspring generation(s).

(iii) Try to integrate the understanding of broader social mechanisms with the understanding of disease specific aetiology to answer the question of how, and to what extent, health inequalities are reproduced into each new generation.

Within this project, we hope to shed light upon some very specific mechanisms how health inequalities are formed over the life-course and regenerated in each new generation. In addition, we hope to be able to inform policy makers about factors that have a long term influence on educational attainment and health, offering new insights for prevention, health promotion and equity in educational attainment.

Study design: construction of the UBCoS Multigenerational database

This unique multigenerational data base was established by combining existing data on a representative and well-defined cohort of all men and women born in Uppsala from 1915-1929 (the Uppsala Birth Cohort: UBCoS) with information on descendants of the original cohort members obtained through a linkage to routine data registers. The primary source of information was a linkage of personal details of 12,168 men and women born in Uppsala from 1915-1929 who were alive and resident in Sweden in 1947, to the Swedish Multigeneration Registry.

The data base currently contains information about families spanning over up to five generations, including the 12,168 original cohort members (generation 1), their 21,070 children, 37,234 grandchildren and 12,900 great grandchildren born up to 2002. For each of the traced subjects, a range of social and health data is available from Censuses, Medical Birth Registry, LOUISE registry, Inpatient registry, Cancer and Death registry and the Conscript registry. Additional, manually collected information on social and early life characteristics is available for the original cohort born 1915-1929 and their parents.

The database is unique in being able to study intergenerational associations as "forward in time" processes, starting in the beginning of the last century, i.e. well before any of the routine registers were in place.

Collaborators

The project is a collaboration between several academic institutions:

- Centre for Health Equity Studies (CHESS), a research institute of the Stockholm University and Karolinska Institute, Sweden.
- Department of Public Health and Caring Sciences at the Uppsala University, Sweden.
- Department of Medical Epidemiology and Biostatistics at Karolinska Institute, Sweden.
- Department of Epidemiology and Population Health at the London School of Hygiene and Tropical Medicine, University of London, UK.

The core team (the Multigen team) is led by Professor Ilona Koupil (CHESS) and consists of senior researchers, research students and administrative

staff whose background and expertise cover a range of disciplines required for the project, namely social medicine and epidemiology, public health medicine, sociology, medical sociology, biostatistics, and data management. The management of the study includes a smaller steering group.

Ethics

The study received a full approval from the regional Ethics committee at Karolinska Institute: dnr 03-117 (2003-03-10) and dnr 04-944T (2004-12-10).

Funding

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PI: Ilona Koupil

Swedish Council for Working Life and Social Research (Forskningsrådet för arbetsliv och socialvetenskap)

Project 2003-0101

"Reproduction of health and health inequality across five generations" ("Sociala skillnader i hälsa. En studie av deras reproduction över fem generationer")

PI: Ilona Koupil

Project 2004-1439

"Life course approach to health equity studies" ("Livsförloppsfaktorers betydelse för hälsa och hälsoojämlikhet")

PI: Ilona Koupil

Centre for Health Equity Studies (CHESS)

A.1.2 UBCOS SUPPLEMENTARY TABLES AND FIGURES

Table A.1.1: Fertility rate ratios for the association between markers of *in utero* growth and age-adjusted fertility rates for all women 15-44, stratified by other variables (tests for interaction calculated using Mantel-Haenszel tests for heterogeneity of ratios)

		Low birthweight		Preterm gestation		Small for gestational age		Low ponderal index	
		FRR (95% CI)	Test for interaction (p value)	FRR (95% CI)	Test for interaction (p value)	FRR (95% CI)	Test for interaction (p value)	FRR (95% CI)	Test for interaction (p value)
Birth characteristics									
Year of birth	1915-1919	0.85 (0.66, 1.11)	0.48	0.92 (0.77, 1.11)	0.8	0.95 (0.81, 1.11)	0.65	0.95 (0.86, 1.06)	0.68
	1920-1924	0.88 (0.73, 1.07)		0.94 (0.82, 1.08)		0.96 (0.85, 1.09)		1.00 (0.92, 1.09)	
	1925-1929	0.99 (0.83, 1.16)		0.98 (0.88, 1.09)		1.02 (0.91, 1.15)		1.01 (0.91, 1.11)	
Mother's civil status	Married	0.91 (0.80, 1.03)	0.89	0.95 (0.86, 1.05)	0.88	0.97 (0.89, 1.05)	0.49	0.93 (0.88, 0.99)	0.07
	Single	0.96 (0.75, 1.25)		0.96 (0.85, 1,09)		1.06 (0.90, 1.26)		1.07 (0.95, 1.21)	
	Divorced/widowed	0.90 (0.70, 1.17)		-		0.89 (0.68, 1.16)		0.90 (0.48, 1.67)	
	Missing								
Residence	Uppsala	0.92 (0.76, 1.12)	0.99	0.97 (0.86, 1.09)	0.92	1.03 (0.93, 1.14)	0.3	0.97 (0.90, 1.05)	0.92
	Other	0.92 (0.80, 1.06)		0.96 (0.87, 1.06)		0.96 (0.86, 1.06)		0.97 (0.90, 1.05)	
	Missing								
Socioeconomic class at birth	higher non-manual	0.80 (0.52, 1.20)	0.38	0.90 (0.61, 1.32)	0.64	1.14 (0.90, 1.44)	0.04	1.00 (0.83, 1.21)	0.14
	medium/lower non-manual	0.89 (0.69, 1.14)		1.00 (0.85, 1.19)		0.87 (0.72, 1.06)		1.02 (0.89, 1.16)	
	farmers or self-employed	0.97 (0.77, 1.24)		0.98 (0.82, 1.16)		0.87 (0.72, 1.06)		1.01 (0.89, 1.14)	
	higher manual	0.69 (0.50, 0.94)		1.06 (0.85, 1.32)		0.93 (0.77, 1.12)		0.80 (0.70, 0.92)	
	lower manual	1.03 (0.86, 1.23)		0.95 (0.82, 1.09)		1.03 (0.93, 1.15)		0.97 (0.88, 1.06)	
	other	0.97 (0.61, 1.53)		0.79 (0.65, 0.96)		1.30 (0.96, 1.78)		1.05 (0.86, 1.29)	
Adult characteristics									
Socioeconomic class at 1960 census (household)	Non-manual	0.97 (0.81, 1.16)	0.91	1.03 (0.93, 1.15)	0.36	0.99 (0.88, 1.11)	0.42	1.00 (0.92, 1.08)	0.64
	Manual	0.93 (0.77, 1.11)		0.91 (0.81, 1.04)		1.04 (0.92, 1.17)		0.97 (0.89, 1.06)	
	Self-employed	0.98 (0.83, 1.15)		0.98 (0.77, 1.24)		0.90 (0.79, 1.03)		0.93 (0.82, 1.05)	
	Missing								
Occupation at 1960 census	In paid work	0.80 (0.62, 1.04)	0.13	1.06 (0.90, 1.26)	0.16	0.98 (0.83, 1.17)	0.94	1.01 (0.90, 1.13)	0.41
	Not in work	0.98 (0.88, 1.10)		0.93 (0.86, 1.01)		0.98 (0.91, 1.06)		0.96 (0.91, 1.02)	
	Missing								

Table A.1.2: Fertility rate ratios for the association between markers of *in utero* growth and age-adjusted fertility rates for all women 15-44, adjusted by potential confounding factors

	Ageband only	Birth cohort and ageband	Mother's civil status and ageband	Residence and ageband	Socio-economic group at birth and ageband
	FRR (95% CI)	FRR (95% CI)	FRR (95% CI)	FRR (95% CI)	FRR (95% CI)
BIRTHWEIGHT					
Low birthweight (<2500g)	0.93 (0.84, 1.03)	0.93 (0.83, 1.04)	0.93 (0.83, 1.04)	0.92 (0.82, 1.03)	0.93 (0.83, 1.04)
GESTATION					
Preterm (<37 weeks)	0.96 (0.88, 1.04)	0.96 (0.88, 1.03)	0.95 (0.88, 1.03)	0.96 (0.89, 1.04)	0.96 (0.88, 1.04)
BWT FOR GESTATIONAL AGE					
<10th centile weight for gestational age	0.99 (0.93, 1.07)	0.99 (0.92, 1.06)	0.99 (0.92, 1.07)	0.99 (0.92, 1.07)	0.99 (0.92, 1.07)
PONDERAL INDEX					
Low ponderal index (lowest quintile)	0.97 (0.92, 1.02)	0.99 (0.94, 1.04)	0.97 (0.92, 1.02)	0.97 (0.92, 1.03)	0.97 (0.92, 1.02)

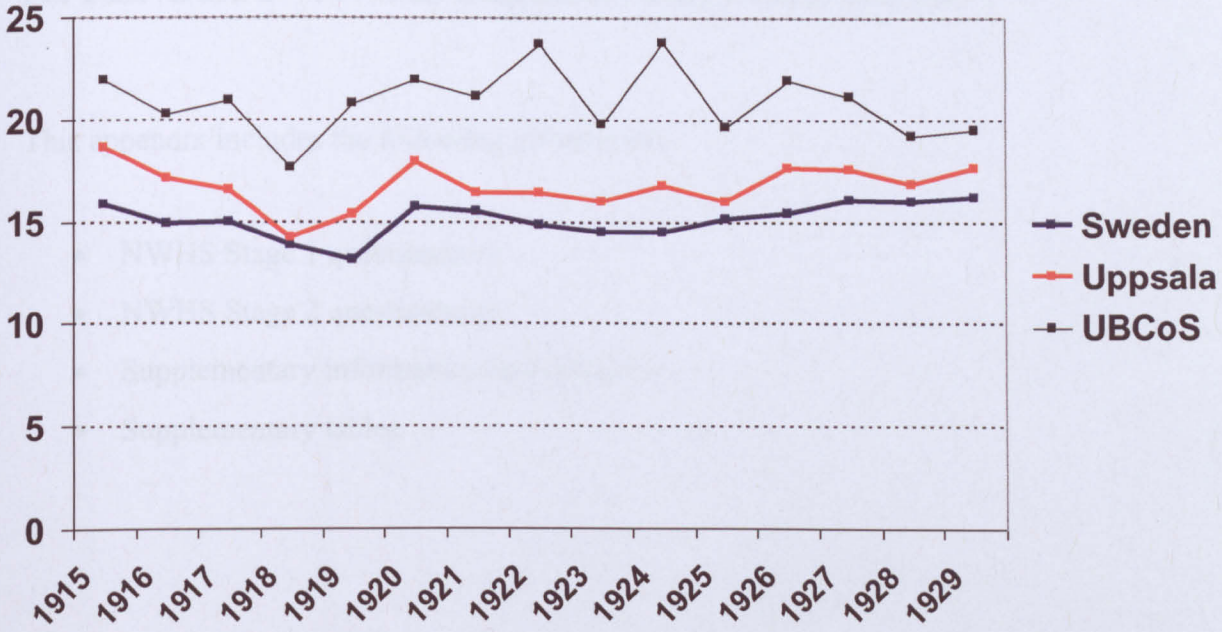
Table A.1.3: Fecundability ratios for the association between markers of *in utero* growth and time to first live birth, stratified by other variables (tests for interaction calculated using Mantel-Haenszel tests for heterogeneity of ratios)

		Low birthweight		Preterm gestation		Small for gestational age		Low ponderal index	
		FR (95% CI)	Test for interaction (p value)	FR (95% CI)	Test for interaction (p value)	FR (95% CI)	Test for interaction (p value)	FR (95% CI)	Test for interaction (p value)
Birth characteristics									
Year of birth	1915-1919	1.09 (0.75, 1.58)	0.29	0.97 (0.74, 1.27)	0.82	1.15 (0.88, 1.50)	0.52	1.03 (0.87, 1.22)	0.59
	1920-1924	1.02 (0.73, 1.42)		0.96 (0.76, 1.22)		0.94 (0.75, 1.18)		0.92 (0.79, 1.07)	
	1925-1929	0.79 (0.61, 1.02)		0.88 (0.70, 1.10)		1.06 (0.88, 1.29)		0.93 (0.79, 1.11)	
Residence	Uppsala	0.81 (0.61, 1.08)	0.24	0.94 (0.78, 1.14)	0.98	1.16 (0.96, 1.40)	0.14	0.97 (0.85, 1.10)	0.42
	Other	1.01 (0.80, 1.27)		0.94 (0.76, 1.16)		0.95 (0.80, 1.13)		0.90 (0.79, 1.02)	
	Missing								
Socioeconomic class at birth	higher non-manual	0.80 (0.39, 1.61)	0.37	1.18 (0.58, 2.40)	0.16	0.88 (0.53, 1.46)	0.57	1.49 (1.03, 2.15)	0.14
	medium/lower non-manual	0.87 (0.57, 1.31)		0.89 (0.65, 1.20)		0.90 (0.65, 1.25)		0.92 (0.74, 1.15)	
	farmers or self-employed	1.06 (0.69, 1.64)		0.92 (0.65, 1.32)		0.96 (0.69, 1.33)		0.87 (0.69, 1.09)	
	higher manual	1.73 (0.99, 3.00)		1.58 (1.08, 2.31)		1.27 (0.93, 1.73)		0.80 (0.03, 1.00)	
	lower manual	0.87 (0.65, 1.18)		0.82 (0.65, 1.04)		1.08 (0.88, 1.33)		0.99 (0.84, 1.16)	
	other	0.77 (0.46, 1.28)		0.88 (0.56, 1.38)		1.30 (0.82, 2.09)		0.90 (0.65, 1.25)	
Adult characteristics									
Age at marriage	<20	1.59 (0.96, 2.63)	0.14	0.83 (0.52, 1.31)	0.80	0.95 (0.68, 1.34)	0.93	1.12 (0.84, 1.49)	0.66
	20-24	0.91 (0.72, 1.45)		0.98 (0.82, 1.18)		1.06 (0.89, 1.26)		0.94 (0.83, 1.06)	
	25-29	0.80 (0.56, 1.15)		0.84 (0.63, 1.12)		1.00 (0.77, 1.30)		0.89 (0.75, 1.06)	
	30-34	2.01 (0.75, 5.43)		0.92 (0.56, 1.52)		1.22 (0.68, 2.20)		1.01 (0.67, 1.51)	
	≥35	2.24 (0.30, 16.49)		2.14 (0.29, 15.7)		0.74 (0.18, 3.13)		0.61 (0.18, 2.02)	
Husband's age at marriage	<25	0.81 (0.61, 1.09)	0.34	0.83 (0.66, 1.04)	0.62	1.05 (0.85, 1.29)	0.28	0.85 (0.73, 1.00)	0.71
	25-29	1.05 (0.81, 1.35)		1.00 (0.81, 1.24)		1.11 (0.91, 1.35)		0.98 (0.85, 1.12)	
	30-34	0.73 (0.40, 1.33)		0.93 (0.65, 1.33)		0.80 (0.55, 1.15)		0.93 (0.73, 1.19)	
	35-39	2.56 (0.63, 10.36)		0.73 (0.23, 2.28)		1.73 (0.93, 3.20)		1.05 (0.67, 1.64)	
	≥40	1.63 (0.50, 5.26)		1.52 (0.60 3.86)		0.83 (0.35, 1.97)		1.06 (0.53, 2.10)	
	Missing								
Socioeconomic class at 1960 census (household)	Non-manual	0.97 (0.81, 1.16)	0.84	0.86 (0.70, 1.04)	0.46	1.10 (0.92, 1.31)	0.70	0.91 (0.80, 1.03)	0.34
	Manual	0.93 (0.77, 1.11)		1.04 (0.82, 1.30)		0.97 (0.77, 1.23)		0.90 (0.76, 1.06)	
	Self-employed	0.98 (0.83, 1.15)		0.95 (0.63, 1.45)		1.10 (0.81, 1.48)		1.09 (0.87, 1.38)	
	Missing								

Table A.1.4: Crude and adjusted fecundability ratios for the association between markers of *in utero* growth and time to first live birth, adjusted by potential confounding factors

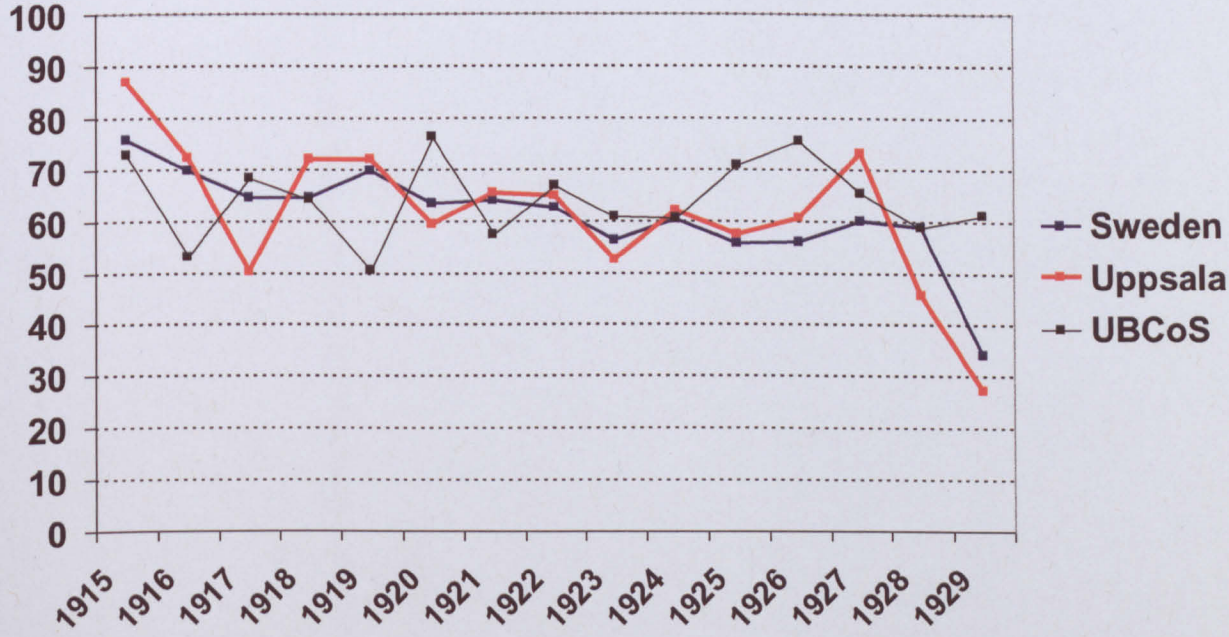
	Crude Fecundability Ratio (95% CI)	Adjusted Fecundability Ratio MODEL 1 (95% CI)	Adjusted Fecundability Ratio MODEL 2 (95% CI)	Adjusted Fecundability Ratio MODEL 3 (95% CI)	Adjusted Fecundability Ratio MODEL 4 (95% CI)	Adjusted Fecundability Ratio MODEL 5 (95% CI)	Adjusted Fecundability Ratio MODEL 6 (95% CI)	FNAL Adjusted Fecundability Ratio FINAL MODEL (95% CI)
Birthweight								
Low <2500g	0.93 (0.78. 1.12)	0.91 (0.76, 1.08)	0.92 (0.77, 1.11)	0.93 (0.78, 1.11)	0.95 (0.77, 1.11)	0.92 (0.77. 1.11)	0.92 (0.77. 1.11)	0.92 (0.77, 1.10)
Normal ≥2500g	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Gestation								
Preterm <37 weeks	0.93 (0.81, 1.07)	0.93 (0.81, 1.07)	0.94 (0.82, 1.08)	0.93 (0.81, 1.07)	0.93 (0.81, 1.07)	0.92 (1.80, 1.06)	0.93 (0.81, 1.07)	0.93 (0.81, 1.07)
Term ≥37 weeks	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Weight for gestational age								
<10th centile	1.05 (0.93, 1.20)	1.04 (0.91, 1.18)	1.04 (0.91, 1.18)	1.05 (0.93, 1.20)	1.03 (0.91, 1.17)	1.05 (0.92, 1.19)	1.06 (0.93, 1.20)	1.03 (0.90, 1.17)
≥10th centile	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Ponderal Index								
Lowest quintile	0.93 (0.85, 1.02)	0.96 (0.87, 1.05)	0.93 (0.85, 1.02)	0.94 (0.85, 1.02)	0.94 (0.86, 1.03)	0.93 (0.85, 1.02)	0.93 (0.85, 1.02)	0.97 (0.88, 1.06)
2nd-5th quintiles	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00

Figure A.1.1: Proportion of live births out of marriage during study period (%)



Source: Statistiska Centralbyrån, Statistisk årsbok för Sverige 1918-1935, kungliga boktryckeriet Norstedt & söner, Stockholm 1918-1935 (reprinted with permission)

Figure A.1.2: Infant mortality: deaths during the first year of life per 1,000 live births during study period



Source: Statistiska centralbyrån Sveriges officiella statistik: Befolkningsrörelsen 1915-1929, Kungliga boktryckeriet. P.A. Norstedt & söner, Stockholm 1919-1932 (reprinted with permission)

APPENDIX 2 NWHS Supplementary information

This appendix includes the following information:

- NWHS Stage 1 questionnaire
- NWHS Stage 2 questionnaire
- Supplementary information on exclusions
- Supplementary tables

A.2.1 NWHS STAGE 1 QUESTIONNAIRE

The National Women's Health Study

Epidemiology Unit, London School of Hygiene & Tropical Medicine, London WC1E 7HT

← Are these details correct?

1 ☐ Yes 0 ☐ No

← If NO, please correct the details on the label

This is a confidential study of pregnancy and fertility

Why have I been sent this form?

You have been selected **at random** from the **UK electoral roll (voting register).** To be scientifically valid the women we are studying need to be typical of all women in the UK. Your response is very important to the success of the study.

I've never tried to get pregnant and I've never been pregnant

If you have never tried to get pregnant we would still like to hear from you (but you need only answer the questions in the white box below).

What is this form about?

This is the first stage of the National Women's Health Study - a **medical survey** of 60,000 women in the UK investigating factors that affect the risk of **miscarriage and infertility**. We need to be able to compare women who have had healthy pregnancies with those whose pregnancies ended in miscarriage or who suffer from infertility, so **even if you have only ever had healthy pregnancies**, your response is still vital to the success of the study.

Who is doing the study?

We are a team of medical researchers from the University of London.

The enclosed leaflet tells you more about the study and the research team.

THIS FORM IS ABOUT PREGNANCY AND FERTILITY IN WOMEN AGED 18 TO 55

If any of the following apply to you, please tick ALL the boxes that apply and return the form to us in the envelope provided. There is no need to fill in the rest of the form:

1 ☐ **I have never tried to get pregnant and I've never been pregnant**

1 ☐ **I am aged over 55**

1 ☐ **I do not want to participate in the study**

If you have NOT ticked any of these boxes, please answer the questions on the next page ⇨

Please do not hesitate to phone us on the Freephone number below if you would like to speak to someone about the survey.

FREEPHONE HELPLINE: 0800 068 3875

We guarantee that all information you give us will be treated with absolute confidentiality and used for medical research only.

THANK YOU VERY MUCH FOR YOUR HELP WITH THIS STUDY

1. What is your date of birth? ☐☐ Day ☐☐ Month ☐☐☐☐ Year *Please just put the year if you do not want to give us your full date of birth*

2. Have you ever been pregnant? 1 ☐ Yes 0 ☐ No → ***Please go to Question 4***

3. Thinking about each of your pregnancies in turn, what was the date each pregnancy ended and the outcome of each pregnancy you have had? *(if exact date not known, please give an approximation)*

First pregnancy	Second pregnancy	Third pregnancy	Fourth pregnancy
☐☐ day ☐☐ month ☐☐☐☐ year (Due date, if pregnant now)	☐☐ day ☐☐ month ☐☐☐☐ year (Due date, if pregnant now)	☐☐ day ☐☐ month ☐☐☐☐ year (Due date, if pregnant now)	☐☐ day ☐☐ month ☐☐☐☐ year (Due date, if pregnant now)
1 ☐ Singleton 2 ☐ Twin 3 ☐ Triplet 4 ☐ Higher 9 ☐ Not known	1 ☐ Singleton 2 ☐ Twin 3 ☐ Triplet 4 ☐ Higher 9 ☐ Not known	1 ☐ Singleton 2 ☐ Twin 3 ☐ Triplet 4 ☐ Higher 9 ☐ Not known	1 ☐ Singleton 2 ☐ Twin 3 ☐ Triplet 4 ☐ Higher 9 ☐ Not known
1 ☐ Liveborn baby 2 ☐ Liveborn baby, but died within 7 days 3 ☐ Stillbirth 4 ☐ Miscarriage 5 ☐ Ectopic 6 ☐ Termination/abortion for medical reasons relating to you or the baby 7 ☐ Termination/abortion for other (non-medical) reasons 8 ☐ Molar pregnancy (hydatidiform mole) 55 ☐ Current pregnancy	1 ☐ Liveborn baby 2 ☐ Liveborn baby, but died within 7 days 3 ☐ Stillbirth 4 ☐ Miscarriage 5 ☐ Ectopic 6 ☐ Termination/abortion for medical reasons relating to you or the baby 7 ☐ Termination/abortion for other (non-medical) reasons 8 ☐ Molar pregnancy (hydatidiform mole) 55 ☐ Current pregnancy	1 ☐ Liveborn baby 2 ☐ Liveborn baby, but died within 7 days 3 ☐ Stillbirth 4 ☐ Miscarriage 5 ☐ Ectopic 6 ☐ Termination/abortion for medical reasons relating to you or the baby 7 ☐ Termination/abortion for other (non-medical) reasons 8 ☐ Molar pregnancy (hydatidiform mole) 55 ☐ Current pregnancy	1 ☐ Liveborn baby 2 ☐ Liveborn baby, but died within 7 days 3 ☐ Stillbirth 4 ☐ Miscarriage 5 ☐ Ectopic 6 ☐ Termination/abortion for medical reasons relating to you or the baby 7 ☐ Termination/abortion for other (non-medical) reasons 8 ☐ Molar pregnancy (hydatidiform mole) 55 ☐ Current pregnancy
Did this pregnancy result from fertility treatment? 1 ☐ Yes 2 ☐ No 1 ☐ Drugs only (e.g. Clomid) 2 ☐ IVF, GIFT or ICSI 3 ☐ AID, AIH or IUI 5 ☐ Other (please describe below)	**Did this pregnancy result from fertility treatment?** 1 ☐ Yes 2 ☐ No 1 ☐ Drugs only (e.g. Clomid) 2 ☐ IVF, GIFT or ICSI 3 ☐ AID, AIH or IUI 5 ☐ Other (please describe below)	**Did this pregnancy result from fertility treatment?** 1 ☐ Yes 2 ☐ No 1 ☐ Drugs only (e.g. Clomid) 2 ☐ IVF, GIFT or ICSI 3 ☐ AID, AIH or IUI 5 ☐ Other (please describe below)	**Did this pregnancy result from fertility treatment?** 1 ☐ Yes 2 ☐ No 1 ☐ Drugs only (e.g. Clomid) 2 ☐ IVF, GIFT or ICSI 3 ☐ AID, AIH or IUI 5 ☐ Other (please describe below)

If you have had more than four pregnancies, please phone Freephone 0800 068 3875 for another form

4. Have you and/or your husband or partner ever consulted a doctor because you were having problems getting pregnant *(i.e you tried for a baby and either didn't succeed in getting pregnant or took a long time to get pregnant)***?**

1 ☐ Yes 0 ☐ No → ***Please go to Question 8***

5. Have you and/or your husband or partner ever had fertility treatment to help you to get pregnant *(e.g. fertility drugs such as Clomid, or treatment such as IVF, ICSI, IUI)***?** 1 ☐ Yes 0 ☐ No → ***Please go to Question 8***

6. If YES, when was the first time you consulted a doctor about fertility problems? *(If exact date not known, please give an approximation)* ☐☐ Day ☐☐ Month ☐☐☐☐ Year

7. If YES, where did you get your treatment?

1 ☐ Treatment from GP only 2 ☐ Treatment by gynaecology / fertility clinic only 3 ☐ Treatment from GP and gynaecology / fertility clinic

This is the first stage of the study. The second stage asks more questions about your pregnancies and fertility.

8. Would you be willing for us to contact you again to take part in the second stage?

1 ☐ Yes, I am willing to be contacted again *(please check the details on the label to ensure they are correct)*

0 ☐ No, please do not contact me again

9. May we contact you by telephone? IF YES, please give telephone numbers below:

DAYTIME TELEPHONE NUMBER:

EVENING TELEPHONE NUMBER:

The National Women's Health Study

A confidential study of pregnancy and fertility

COMMUNITY FUND
Lottery money making a difference

Epidemiology Unit, London School of Hygiene & Tropical Medicine, London WC1E 7HT

← Are these details still correct?

1 ☐ Yes 0 ☐ No

↓

← If NO, please supply the correct the details at the bottom of page 23

Thank you very much for taking part in the first stage of the National Women's Health Study, and for agreeing to participate in the second stage. We would be grateful if you would now complete this questionnaire, which asks more detailed questions.

The National Women's Health Study is a medical survey of 60,000 women in the UK which is investigating factors that affect the risk of miscarriage and infertility. We need to be able to compare women who have had healthy pregnancies with those whose pregnancies ended in miscarriage or who suffer from infertility, so **even if you have only ever had healthy pregnancies, your response is still vital to the success of the study.**

IT IS VERY IMPORTANT THAT YOU RETURN THE QUESTIONNAIRE SO THAT WE KNOW YOU HAVE RECEIVED IT

If you no longer wish to participate in this second stage, please return the blank questionnaire to us in the reply-paid envelope provided, or telephone us using the Freephone number below

We guarantee that all information you give us will be treated with absolute confidentiality and used for medical research only

The information leaflet sent with the first questionnaire provides more information on the study and the research team. Please do not hesitate to phone us on the Freephone number below if you would like to speak to someone about the survey, or would like another information leaflet.

FREEPHONE HELPLINE: 0800 068 3875

Thank you for helping us with this important research

GENERAL QUESTIONS ABOUT YOU

1. What is your date of birth? ☐☐ Day ☐☐ Month ☐☐☐☐ Year

2. How tall are you? ☐☐.☐ feet inches **OR** ☐☐☐ cms

3. What is your shoe size (this relates to your bone structure)? ☐☐.☐ UK **OR** ☐☐ continental

4. What is the highest qualification that you have?

1 ☐ No formal qualifications
2 ☐ CSE, 'O' level, GCSE, RSA secretarial, NVQ1 or 2, Foundation or Intermediate GNVQ, or equivalent
3 ☐ 'A' level, ONC, City & Guilds, EN, NNEB, BTEC, NVQ3, advanced GNVQ, or equivalent
4 ☐ College/university degree, HND, RGN, Teaching Certificate, NVQ4 or 5, OND, or equivalent

5. Have you <u>ever</u> smoked cigarettes regularly *(at least one per day)* for a month or longer?

1 ☐ Yes 0 ☐ No, *please go to* ***question 8***

If YES, when did you first start smoking? ☐☐ Month ☐☐☐☐ Year **OR** 9 ☐ *Don't remember*

6. On average, how many cigarettes do you (or did you use to) smoke PER DAY?

1 ☐ Less than 5 2 ☐ 5-10 3 ☐ 11-20 4 ☐ 21-30 5 ☐ 31 or more **OR** 9 ☐ *Don't know*

7. Do you still smoke? 0 ☐ No 5 ☐ No longer smoke regularly, but still have an occasional cigarette 1 ☐ Yes still smoke, *please go to* ***question 8***

If NO (or you no longer smoke regularly) when did you give up?

☐☐ Month ☐☐☐☐ Year **OR** 9 ☐ *Don't remember*

QUESTIONS ABOUT FERTILITY

8. Have you ever had any problems trying to get pregnant? *(i.e you tried for a baby and either didn't succeed in getting pregnant or took a long time to get pregnant)*

1 ☐ Yes 0 ☐ No, *please go to* ***question 10***

If YES, when did you first start trying to get pregnant (the first time this happened)?

☐☐ Month ☐☐☐☐ Year

9. Did you consult a doctor because you could not get pregnant?

1 ☐ Yes 0 ☐ No

If YES, when was the first time you went to the doctor about this?

☐☐ Month ☐☐☐☐ Year

QUESTIONS ABOUT FERTILITY

10. Have you and/or your husband or partner ever had investigations for infertility?

1 ☐ Yes 0 ☐ No, *please go to next question*

If YES, please could you tell us what the diagnosis was ***(please tick all that apply below):***

YOU	YOUR HUSBAND OR PARTNER
1 ☐ Not ovulating / infrequent ovulation	1 ☐ Low sperm count
1 ☐ Blocked fallopian tubes / tubal damage	1 ☐ No sperm
1 ☐ Endometriosis	1 ☐ Large number of abnormal or dead sperm
1 ☐ Unsuccessful reversal of sterilisation	1 ☐ Slow moving sperm (low motility)
1 ☐ Investigated, but no problems found	1 ☐ Sperm antibodies
1 ☐ Other (please give details)	1 ☐ Unsuccessful reversal of vasectomy
_____	1 ☐ Investigated, but no problems found
_____	1 ☐ Other (please give details)
5 ☐ Not investigated (i.e. only husband/partner investigated)	_____
6 ☐ Still being investigated	_____
9 ☐ *Don't know / don't remember*	5 ☐ Not investigated (i.e. only you were investigated)
	6 ☐ Still being investigated
	9 ☐ *Don't know / don't remember*

11. Have you and/or your husband or partner ever had fertility treatment to help you to get pregnant?

1 ☐ Yes 0 ☐ No, *please go to* ***question 13***

If YES, were you given this treatment *only* by your GP, or did you also attend a hospital gynaecology department or fertility clinic?

1 ☐ GP only 2 ☐ Gynaecology / fertility clinic (and GP) 9 ☐ *Don't know / don't remember*

12. What treatment did you and/or your partner receive? *(please tick all that apply)*

1 ☐ Clomid (Clomiphene, "fertility drugs") *only*, prescribed by GP

1 ☐ Clomid (Clomiphene, "fertility drugs") *only*, prescribed by gynaecology/fertility clinic

1 ☐ IVF or ICSI using natural cycle with NO drugs to induce ovulation (but with or without HCG)

1 ☐ IVF or ICSI with drugs to induce ovulation

1 ☐ AID, AIH or IUI with drugs to induce ovulation

1 ☐ AID, AIH or IUI with NO drugs to induce ovulation (but with or without HCG)

1 ☐ Other assisted reproduction (e.g. GIFT) with NO drugs to induce ovulation (but with or without HCG)

1 ☐ Other assisted reproduction (e.g. GIFT) with drugs to induce ovulation

1 ☐ Other (please give details) _____

9 ☐ *Don't know / don't remember*

QUESTIONS ABOUT PREGNANCY

13. How old were you when your periods started?

☐☐ years OR 9☐ *Don't remember*

14. Have you ever been pregnant?

1☐ Yes 0☐ No, *please go to* ***page 23***

15. Are you pregnant at the moment? 1☐ Yes 0☐ No, *please go to question* ***16 on the next page***

If YES, when is the baby due?

☐☐ Day ☐☐ Month ☐☐☐☐ Year

The next section asks about each of your pregnancies in turn

If you have had more than six pregnancies, please call the Freephone number for an extra form

- **If you cannot remember any of the information we are asking for exactly, please give us an approximation (and mark that you have done this)**

- **If you have any queries about any of the questions, please call us on**

Freephone 0800 068 3875

If any of your pregnancies was a multiple pregnancy, please fill in one column for each baby (if appropriate)

THIS SECTION ASKS ABOUT YOU AND YOUR PREGNANCIES

If you have had more than six pregnancies, please call Freephone number for an extra form

16. Thinking about each of your pregnancies in turn, please could you answer the following questions:	First pregnancy	Second pregnancy
a. **What was the date of birth, or date the pregnancy ended?** *(if exact date not known please give an approximation)*	day month year **(Due date, if pregnant now)**	day month year **(Due date, if pregnant now)**
b. **What was the outcome of the pregnancy?** * ***Including missed abortion and blighted ovum (anembryonic pregnancy)***	1 Liveborn baby 2 Liveborn baby, but died within 7 days 3 Stillbirth 4 Miscarriage* 5 Ectopic 6 Termination/abortion for medical reasons relating to you or the baby 7 Termination/abortion for other (non-medical) reasons 8 Molar pregnancy (hydatidiform mole) 55 Current pregnancy	1 Liveborn baby 2 Liveborn baby, but died within 7 days 3 Stillbirth 4 Miscarriage* 5 Ectopic 6 Termination/abortion for medical reasons relating to you or the baby 7 Termination/abortion for other (non-medical) reasons 8 Molar pregnancy (hydatidiform mole) 55 Current pregnancy
c. **Was this a multiple pregnancy?** → **If YES, please fill in one pregnancy column per baby** *(please phone Freephone 0800 068 3875 if you are unclear about how to fill in this section)*	1 No, singleton 2 Yes, Twin 3 Yes, Triplet 4 Yes, higher number 9 Don't know	1 No, singleton 2 Yes, Twin 3 Yes, Triplet 4 Yes, higher number 9 Don't know
d. **What was the sex of the baby (if known)?**	1 Boy 2 Girl 9 Not known	1 Boy 2 Girl 9 Not known
e. **How many weeks were you when the pregnancy ended (i.e. weeks of gestation)?** *(please put what you were told by the medical staff. If you were not told, please count the number of weeks from the first day of the last period that you had before you got pregnant. A full term (due date) pregnancy is 40 weeks)*	weeks (+ days,) if known **(Current gestation, if pregnant now)** 99 Don't remember	weeks (+ days,) if known **(Current gestation, if pregnant now)** 99 Don't remember
f. **What was the weight of the baby (if applicable)?**	lbs ozs OR grams 7 Not known / Not applicable	lbs ozs OR grams 7 Not known / Not applicable
g. **How old were you when the pregnancy ended?**	Years	Years
h. **What was the date of birth of the father of this pregnancy?** *(if actual date not known, please give the approximate year he was born. Please tick "same father" if father is the same as for previous pregnancy)*	day month year 9 Don't know	6 Same father day month year 9 Don't know
i. **Was the pregnancy confirmed:** **(1) by a pregnancy test?** **(2) by an ultrasound scan?**	1 Yes 0 No 9 Don't remember 1 Yes 0 No 9 Don't remember **Please turn page for more questions about this pregnancy**	1 Yes 0 No 9 Don't remember 1 Yes 0 No 9 Don't remember **Please turn page for more questions about this pregnancy**

THIS SECTION ASKS ABOUT YOU AND YOUR PREGNANCIES

If you have had more than six pregnancies, please call Freephone number for an extra form

Third pregnancy	Fourth pregnancy	Fifth pregnancy	Sixth pregnancy
day month year **(Due date, if pregnant now)**	day month year **(Due date, if pregnant now)**	day month year **(Due date, if pregnant now)**	day month year **(Due date, if pregnant now)**
1 Liveborn baby 2 Liveborn baby, but died within 7 days 3 Stillbirth 4 Miscarriage* 5 Ectopic 6 Termination/abortion for medical reasons relating to you or the baby 7 Termination/abortion for other (non-medical) reasons 8 Molar pregnancy (hydatidiform mole) 55 Current pregnancy	1 Liveborn baby 2 Liveborn baby, but died within 7 days 3 Stillbirth 4 Miscarriage* 5 Ectopic 6 Termination/abortion for medical reasons relating to you or the baby 7 Termination/abortion for other (non-medical) reasons 8 Molar pregnancy (hydatidiform mole) 55 Current pregnancy	1 Liveborn baby 2 Liveborn baby, but died within 7 days 3 Stillbirth 4 Miscarriage* 5 Ectopic 6 Termination/abortion for medical reasons relating to you or the baby 7 Termination/abortion for other (non-medical) reasons 8 Molar pregnancy (hydatidiform mole) 55 Current pregnancy	1 Liveborn baby 2 Liveborn baby, but died within 7 days 3 Stillbirth 4 Miscarriage* 5 Ectopic 6 Termination/abortion for medical reasons relating to you or the baby 7 Termination/abortion for other (non-medical) reasons 8 Molar pregnancy (hydatidiform mole) 55 Current pregnancy
1 No, singleton 2 Yes, Twin 3 Yes, Triplet 4 Yes, higher number 9 Don't know	1 No, singleton 2 Yes, Twin 3 Yes, Triplet 4 Yes, higher number 9 Don't know	1 No, singleton 2 Yes, Twin 3 Yes, Triplet 4 Yes, higher number 9 Don't know	1 No, singleton 2 Yes, Twin 3 Yes, Triplet 4 Yes, higher number 9 Don't know
1 Boy 2 Girl 9 Not known	1 Boy 2 Girl 9 Not known	1 Boy 2 Girl 9 Not known	1 Boy 2 Girl 9 Not known
weeks (+ days, if known) **(Current gestation, if pregnant now)** 99 Don't remember	weeks (+ days, if known) **(Current gestation, if pregnant now)** 99 Don't remember	weeks (+ days, if known) **(Current gestation, if pregnant now)** 99 Don't remember	weeks (+ days, if known) **(Current gestation, if pregnant now)** 99 Don't remember
lbs ozs OR grams 7 Not known / Not applicable	lbs ozs OR grams 7 Not known / Not applicable	lbs ozs OR grams 7 Not known / Not applicable	lbs ozs OR grams 7 Not known / Not applicable
Years	Years	Years	Years
6 Same father day month year 9 Don't know	6 Same father day month year 9 Don't know	6 Same father day month year 9 Don't know	6 Same father day month year 9 Don't know
1 Yes 0 No 9 Don't remember 1 Yes 0 No 9 Don't remember	1 Yes 0 No 9 Don't remember 1 Yes 0 No 9 Don't remember	1 Yes 0 No 9 Don't remember 1 Yes 0 No 9 Don't remember	1 Yes 0 No 9 Don't remember 1 Yes 0 No 9 Don't remember
Please turn page for more questions about this pregnancy	**Please turn page for more questions about this pregnancy**	**Please turn page for more questions about this pregnancy**	**Please turn page for more questions about this pregnancy**

THIS SECTION ASKS ABOUT YOU AND YOUR PREGNANCIES

If you have had more than six pregnancies, please call Freephone number for an extra form

	First pregnancy	Second pregnancy
j. Were you attended by a doctor or midwife when the pregnancy ended?	1 ☐ Yes 0 ☐ No 9 ☐ Don't remember	1 ☐ Yes 0 ☐ No 9 ☐ Don't remember
k. Was this pregnancy planned?	1 ☐ Yes 0 ☐ No 9 ☐ Don't remember	1 ☐ Yes 0 ☐ No 9 ☐ Don't remember
→ If YES, how long did you try before you got pregnant?	1 ☐ Less than 3 months 2 ☐ 3 to 6 months 3 ☐ 7 to 12 months 4 ☐ More than 12 months 9 ☐ Don't remember	1 ☐ Less than 3 months 2 ☐ 3 to 6 months 3 ☐ 7 to 12 months 4 ☐ More than 12 months 9 ☐ Don't remember
l. Did this pregnancy result from fertility treatment?	1 ☐ Yes 0 ☐ No 9 ☐ Don't remember	1 ☐ Yes 0 ☐ No 9 ☐ Don't remember
→ If YES, please tick the type of fertility treatment you had	1 ☐ Drugs only (e.g. Clomid) 2 ☐ IVF, GIFT or ICSI 3 ☐ AID, AIH, IUI with drugs to induce ovulation 4 ☐ AID, AIH, IUI without drugs to induce ovulation 5 ☐ Other (please specify) _____	1 ☐ Drugs only (e.g. Clomid) 2 ☐ IVF, GIFT or ICSI 3 ☐ AID, AIH, IUI with drugs to induce ovulation 4 ☐ AID, AIH, IUI without drugs to induce ovulation 5 ☐ Other (please specify) _____
m. Were any abnormalities detected in the baby, either during the pregnancy or after birth?	1 ☐ Yes 2 ☐ No 9 ☐ Not known	1 ☐ Yes 2 ☐ No 9 ☐ Not known
→ If YES, please could you describe the problem/s:		
→ If YES, please could you give us the name and town of the hospital/s you attended regarding the problem/s:		
n. Were you diagnosed with any health problems or given any medical treatment during this pregnancy?	1 ☐ Yes 2 ☐ No 9 ☐ Not known	1 ☐ Yes 2 ☐ No 9 ☐ Not known
→ If YES, please could you describe the problem/s or treatment/s:		
→ If YES, please could you give us the name and town of the hospital/s you attended regarding the problem/s:		
	Please continue onto next pregnancy, or to Question 17 if no more pregnancies	Please continue onto next pregnancy, or to Question 17 if no more pregnancies

THIS SECTION ASKS ABOUT YOU AND YOUR PREGNANCIES

If you have had more than six pregnancies, please call Freephone number for an extra form

Third pregnancy	Fourth pregnancy	Fifth pregnancy	Sixth pregnancy
1 Yes 0 No 9 Don't remember	1 Yes 0 No 9 Don't remember	1 Yes 0 No 9 Don't remember	1 Yes 0 No 9 Don't remember
1 Yes 0 No 9 Don't remember 1 Less than 3 months 2 3 to 6 months 3 7 to 12 months 4 More than 12 months 9 Don't remember	1 Yes 0 No 9 Don't remember 1 Less than 3 months 2 3 to 6 months 3 7 to 12 months 4 More than 12 months 9 Don't remember	1 Yes 0 No 9 Don't remember 1 Less than 3 months 2 3 to 6 months 3 7 to 12 months 4 More than 12 months 9 Don't remember	1 Yes 0 No 9 Don't remember 1 Less than 3 months 2 3 to 6 months 3 7 to 12 months 4 More than 12 months 9 Don't remember
1 Yes 0 No 9 Don't remember 1 Drugs only (e.g. Clomid) 2 IVF, GIFT or ICSI 3 AID, AIH, IUI with drugs to induce ovulation 4 AID, AIH, IUI without drugs to induce ovulation 5 Other (please specify) _____	1 Yes 0 No 9 Don't remember 1 Drugs only (e.g. Clomid) 2 IVF, GIFT or ICSI 3 AID, AIH, IUI with drugs to induce ovulation 4 AID, AIH, IUI without drugs to induce ovulation 5 Other (please specify) _____	1 Yes 0 No 9 Don't remember 1 Drugs only (e.g. Clomid) 2 IVF, GIFT or ICSI 3 AID, AIH, IUI with drugs to induce ovulation 4 AID, AIH, IUI without drugs to induce ovulation 5 Other (please specify) _____	1 Yes 0 No 9 Don't remember 1 Drugs only (e.g. Clomid) 2 IVF, GIFT or ICSI 3 AID, AIH, IUI with drugs to induce ovulation 4 AID, AIH, IUI without drugs to induce ovulation 5 Other (please specify) _____
1 Yes 2 No 9 Not known	1 Yes 2 No 9 Not known	1 Yes 2 No 9 Not known	1 Yes 2 No 9 Not known
1 Yes 2 No 9 Not known	1 Yes 2 No 9 Not known	1 Yes 2 No 9 Not known	1 Yes 2 No 9 Not known
Please continue onto next pregnancy, or to Question 17 if no more pregnancies	**Please continue onto next pregnancy, or to Question 17 if no more pregnancies**	**Please continue onto next pregnancy, or to Question 17 if no more pregnancies**	**Please continue onto next pregnancy, or to Question 17 if no more pregnancies**

QUESTIONS ABOUT YOUR *LAST PREGNANCY*

We would now like to concentrate only on **your LAST pregnancy.** This may have ended with a liveborn baby, or you may have lost the baby. We will ask you a series of questions relating to the **three months before** your last pregnancy **(counting back from the first day of the last period you had before you were pregnant),** and about the **first twelve weeks** of the pregnancy **(counting forwards from the first day of the last period you had before you became pregnant).**

If you are currently 24 or more weeks pregnant, please tell us about your current pregnancy. Otherwise please tell us about your last pregnancy. *If you are unclear about how to fill in this section please phone Freephone 0800 068 3875.*

Please confirm below the date your LAST pregnancy ended *(or due date if currently 24 or more weeks pregnant)*. This is the ONLY pregnancy we shall be asking about from now on.

☐☐ Day ☐☐ Month ☐☐☐☐ Year

17. What was your weight in the 3 months before your last pregnancy began *(if you cannot remember exactly, please give an approximation)*?

☐☐ stone ☐☐ lb **OR** ☐☐☐ kg 9 ☐ *Don't remember*

18. How would you best describe your relationship status during your last pregnancy?

1 ☐ Single, separated or divorced and living with adult friends or family
2 ☐ Single, separated or divorced and living alone or with children
3 ☐ Married or living together
4 ☐ Other

19. Did you experience any nausea (feeling sick) or vomiting in your last pregnancy?

1 ☐ Yes 0 ☐ No 9 ☐ *Don't remember*

If YES, how severe was the sickness, and when did you experience it? *(please tick how you felt in each 12-week period)*

DEFINITIONS: **Mild:** feeling sick only **Moderate:** feeling sick and sometimes vomiting **Severe:** frequent vomiting, couldn't retain meals

First 12 weeks (First trimester)	**Second 12 weeks** (Second trimester)	**Remainder of pregnancy** (Third trimester)
1 ☐ Mild	1 ☐ Mild	1 ☐ Mild
2 ☐ Moderate	2 ☐ Moderate	2 ☐ Moderate
3 ☐ Severe, but was not hospitalised	3 ☐ Severe, but was not hospitalised	3 ☐ Severe, but was not hospitalised
4 ☐ Severe, had to be hospitalised	4 ☐ Severe, had to be hospitalised	4 ☐ Severe, had to be hospitalised
7 ☐ No sickness in this time period	7 ☐ No sickness in this time period	7 ☐ No sickness in this time period
9 ☐ *Don't remember*	9 ☐ *Don't remember / Not applicable*	9 ☐ *Don't remember / Not applicable*

20. Where were you living in the 3 months before and in the first 12 weeks of your last pregnancy?
(please answer for both time periods)

In the 3 MONTHS BEFORE your last pregnancy

Town _____

County _____

Postcode (if known) ☐☐☐☐ ☐☐☐

1 ☐ Please tick the box if this address is outside the UK

9 ☐ *Don't remember*

In the FIRST 12 WEEKS of your last pregnancy

6 ☐ Same address as in the 3 months before I became pregnant

OR

Town _____

County _____

Postcode (if known) ☐☐☐☐ ☐☐☐

1 ☐ Please tick the box if this address is outside the UK

9 ☐ *Don't remember*

QUESTIONS ABOUT DIET IN YOUR *LAST PREGNANCY*

21. Did you take any vitamins, minerals or supplements EVERY DAY for a period of ONE WEEK OR MORE either in the 3 months before or in the first 12 weeks of your last pregnancy? *(please tick all that apply in each time period)*

In the 3 MONTHS BEFORE your last pregnancy	In the FIRST 12 WEEKS of your last pregnancy
0 ☐ No, did not take anything at this time	0 ☐ No, did not take anything at this time
YES, I TOOK THE FOLLOWING:	YES, I TOOK THE FOLLOWING:
1 ☐ Pregnancy preparation (e.g. *Pregnacare*)	1 ☐ Pregnancy preparation (e.g. *Pregnacare*)
1 ☐ Multivitamins with minerals	1 ☐ Multivitamins with minerals
1 ☐ Multivitamins with no minerals	1 ☐ Multivitamins with no minerals
1 ☐ Folic acid	1 ☐ Folic acid
1 ☐ Iron	1 ☐ Iron
1 ☐ Zinc	1 ☐ Zinc
1 ☐ Vitamin C	1 ☐ Vitamin C
1 ☐ *Foresight* / nutritional program following testing of hair or blood	1 ☐ *Foresight* / nutritional program following testing of hair or blood
1 ☐ Others *(please give details)* _____	1 ☐ Others *(please give details)* _____
_____	_____
9 ☐ *Don't know / don't remember*	9 ☐ *Don't know / don't remember*

22. Were you a vegan or vegetarian either in the 3 months before or in the first 12 weeks of your last pregnancy? *(please answer for both time periods)*

In the 3 MONTHS BEFORE your last pregnancy	In the FIRST 12 WEEKS of your last pregnancy
0 ☐ No, I was not a vegan or vegetarian	0 ☐ No, I was not a vegan or vegetarian
YES, I WAS THE FOLLOWING:	YES, I WAS THE FOLLOWING:
1 ☐ Vegan	1 ☐ Vegan
2 ☐ Vegetarian	2 ☐ Vegetarian
3 ☐ Mainly vegetarian, but ate fish	3 ☐ Mainly vegetarian, but ate fish
9 ☐ *Don't know / don't remember*	9 ☐ *Don't know / don't remember*

23. Were you on a special diet either in the 3 months before or in the first 12 weeks of your last pregnancy? *(please answer for both time periods, and tick more than one if it applies)*

In the 3 MONTHS BEFORE your last pregnancy	In the FIRST 12 WEEKS of your last pregnancy
0 ☐ No, I was not on a special diet	0 ☐ No, I was not on a special diet
YES, I WAS ON THE FOLLOWING DIET(S)	YES, I WAS ON THE FOLLOWING DIET(S)
1 ☐ Gluten-free	1 ☐ Gluten-free
1 ☐ Diabetic	1 ☐ Diabetic
1 ☐ Lactose-free	1 ☐ Lactose-free
1 ☐ Low salt	1 ☐ Low salt
1 ☐ Low fat	1 ☐ Low fat
1 ☐ Other *(please give details)* _____	1 ☐ Other *(please give details)* _____
_____	_____
9 ☐ *Don't know / don't remember*	9 ☐ *Don't know / don't remember*

QUESTIONS ABOUT DIET IN YOUR *LAST PREGNANCY*

24. Please tick below the foods you ate twice or more per week in the 3 months before and in the first 12 weeks of your last pregnancy? *(please answer for both time periods, and tick all that apply)*

In the 3 MONTHS BEFORE your last pregnancy	In the FIRST 12 WEEKS of your last pregnancy
I ATE THE FOLLOWING TWICE A WEEK OR MORE:	I ATE THE FOLLOWING TWICE A WEEK OR MORE:
1 ☐ Red meat (e.g. lamb, beef, pork)	1 ☐ Red meat (e.g. lamb, beef, pork)
1 ☐ White meat (e.g. chicken, turkey)	1 ☐ White meat (e.g. chicken, turkey)
1 ☐ Fish	1 ☐ Fish
1 ☐ Eggs	1 ☐ Eggs
0 ☐ ATE NONE OF THESE FOODS TWICE A WEEK OR MORE	0 ☐ ATE NONE OF THESE FOODS TWICE A WEEK OR MORE
9 ☐ *Don't know / don't remember*	9 ☐ *Don't know / don't remember*

25. Please tick below the foods you ate EVERY DAY OR MOST DAYS in the 3 months before and in the first 12 weeks of your last pregnancy? *(please answer for both time periods, and tick all that apply)*

In the 3 MONTHS BEFORE your last pregnancy	In the FIRST 12 WEEKS of your last pregnancy
I ATE THE FOLLOWING EVERY DAY OR MOST DAYS:	I ATE THE FOLLOWING EVERY DAY OR MOST DAYS:
1 ☐ Fresh fruit (ordinary)	1 ☐ Fresh fruit (ordinary)
1 ☐ Fresh fruit (organic)	1 ☐ Fresh fruit (organic)
1 ☐ Fresh vegetables (ordinary)	1 ☐ Fresh vegetables (ordinary)
1 ☐ Fresh vegetables (organic)	1 ☐ Fresh vegetables (organic)
1 ☐ Dairy products (e.g. milk, cheese, yoghurt)	1 ☐ Dairy products (e.g. milk, cheese, yoghurt)
1 ☐ Soya products (e.g. soya milk or yoghurt, tofu)	1 ☐ Soya products (e.g. soya milk or yoghurt, tofu)
1 ☐ Sugar substitutes (e.g. Canderel, diet drinks and foods)	1 ☐ Sugar substitutes (e.g. Canderel, diet drinks and foods)
1 ☐ Chocolate (food or drink)	1 ☐ Chocolate (food or drink)
0 ☐ ATE NONE OF THESE FOODS EVERY DAY OR MOST DAYS	0 ☐ ATE NONE OF THESE FOODS EVERY DAY OR MOST DAYS
9 ☐ *Don't know / don't remember*	9 ☐ *Don't know / don't remember*

26. Did you eat any of the following foods at all in the 3 months before or in the first 12 weeks of your last pregnancy? *(please answer for both time periods, and tick all that apply)*

In the 3 MONTHS BEFORE your last pregnancy	In the FIRST 12 WEEKS of your last pregnancy
1 ☐ Unpasteurised food (e.g. unpasteurised cheese or milk)	1 ☐ Unpasteurised food (e.g. unpasteurised cheese or milk)
1 ☐ Rare (undercooked) meat *including chicken*	1 ☐ Rare (undercooked) meat *including chicken*
1 ☐ Shellfish (e.g. mussels) or prawns, shrimps, lobster	1 ☐ Shellfish (e.g. mussels) or prawns, shrimps, lobster
1 ☐ Paté	1 ☐ Paté
1 ☐ Raw eggs (e.g. in fresh mayonnaise)	1 ☐ Raw eggs (e.g. in fresh mayonnaise)
1 ☐ Eggs with a soft yolk (e.g. soft-boiled eggs)	1 ☐ Eggs with a soft yolk (e.g. soft-boiled eggs)
0 ☐ ATE NONE OF THESE FOODS	0 ☐ ATE NONE OF THESE FOODS
9 ☐ *Don't know / don't remember*	9 ☐ *Don't know / don't remember*

QUESTIONS ABOUT DIET IN YOUR *LAST PREGNANCY*

27. Were there any foods, drinks or other substances that you ATE ALL THE TIME or CRAVED in the first 12 weeks of your last pregnancy?

In the FIRST 12 WEEKS of your last pregnancy

1 ☐ Yes ↓ 0 ☐ No 9 ☐ *Don't remember*

If YES, please give details: _____

28. Were there any foods or drinks that you NEVER TOUCHED because you FOUND THEM REPULSIVE in the first 12 weeks of your last pregnancy?

In the FIRST 12 WEEKS of your last pregnancy

1 ☐ Yes ↓ 0 ☐ No 9 ☐ *Don't remember*

If YES, please give details: _____

29. How many CAFFEINATED DRINKS did you drink PER DAY in the 3 months before and in the first 12 weeks of your last pregnancy? *(please answer for both time periods, and for each type of drink)*

In the 3 MONTHS BEFORE your last pregnancy	In the FIRST 12 WEEKS of your last pregnancy
COFFEE (mugs per day):	***COFFEE (mugs per day):***
0 ☐ None 1 ☐ Less than 1 2 ☐ 1 - 2 3 ☐ 3 - 4	0 ☐ None 1 ☐ Less than 1 2 ☐ 1 - 2 3 ☐ 3 - 4
4 ☐ 5 - 9 5 ☐ 10 or more 9 ☐ *Don't remember*	4 ☐ 5 - 9 5 ☐ 10 or more 9 ☐ *Don't remember*
TEA (mugs per day):	***TEA (mugs per day):***
0 ☐ None 1 ☐ Less than 1 2 ☐ 1 - 2 3 ☐ 3 - 4	0 ☐ None 1 ☐ Less than 1 2 ☐ 1 - 2 3 ☐ 3 - 4
4 ☐ 5 - 9 5 ☐ 10 or more 9 ☐ *Don't remember*	4 ☐ 5 - 9 5 ☐ 10 or more 9 ☐ *Don't remember*
OTHER CAFFEINATED DRINKS, e.g. Coca Cola, Red Bull (cans per day):	***OTHER CAFFEINATED DRINKS, e.g. Coca Cola, Red Bull (cans per day):***
0 ☐ None 1 ☐ Less than 1 2 ☐ 1 - 2 3 ☐ 3 - 4	0 ☐ None 1 ☐ Less than 1 2 ☐ 1 - 2 3 ☐ 3 - 4
4 ☐ 5 - 9 5 ☐ 10 or more 9 ☐ *Don't remember*	4 ☐ 5 - 9 5 ☐ 10 or more 9 ☐ *Don't remember*

30. On average, how often did you drink ALCOHOL in the 3 months before and in the first 12 weeks of your last pregnancy? *(please answer for both time periods)*

In the 3 MONTHS BEFORE your last pregnancy	In the FIRST 12 WEEKS of your last pregnancy
77 ☐ Had never drunk alcohol (teetotal), ***please go to question 33***	
1 ☐ Every day	1 ☐ Every day
2 ☐ Three or more days during the week and at weekends	2 ☐ Three or more days during the week and at weekends
3 ☐ Two days or less during the week and at weekends	3 ☐ Two days or less during the week and at weekends
4 ☐ Weekends only	4 ☐ Weekends only
5 ☐ Less than once a week	5 ☐ Less than once a week
6 ☐ Special occasions only	6 ☐ Special occasions only
	7 ☐ Stopped when I found out I was pregnant at ☐☐ weeks
0 ☐ Did not drink alcohol at all during these 3 months	0 ☐ Did not drink alcohol at all during the first 12 weeks
9 ☐ *Don't know / don't remember*	9 ☐ *Don't know / don't remember*

QUESTIONS ABOUT YOUR LIFESTYLE IN YOUR *LAST PREGNANCY*

31. How much of each of the following ALCOHOLIC DRINKS did you drink ON AVERAGE BETWEEN MONDAY AND THURSDAY? *(please answer for both time periods, and for each type of drink)*

In the 3 MONTHS BEFORE your last pregnancy	In the FIRST 12 WEEKS of your last pregnancy
0 ☐ Did not drink alcohol at all during these 3 months	0 ☐ Did not drink alcohol at all during the first 12 weeks
ON AVERAGE I DRANK THE FOLLOWING BETWEEN MONDAY AND THURSDAY (IN TOTAL):	ON AVERAGE I DRANK THE FOLLOWING BETWEEN MONDAY AND THURSDAY (IN TOTAL) *(until you stopped, if appropriate)*:
Beer, Lager, Cider ☐☐ pints 9 ☐ *Don't remember*	Beer, Lager, Cider ☐☐ pints 9 ☐ *Don't remember*
Wine ☐☐ glasses 9 ☐ *Don't remember*	Wine ☐☐ glasses 9 ☐ *Don't remember*
Martini, Sherry, Port ☐☐ glasses 9 ☐ *Don't remember*	Martini, Sherry, Port ☐☐ glasses 9 ☐ *Don't remember*
Spirits ☐☐ measures 9 ☐ *Don't remember*	Spirits ☐☐ measures 9 ☐ *Don't remember*
Other alcoholic drinks ☐☐ glasses 9 ☐ *Don't remember*	Other alcoholic drinks ☐☐ glasses 9 ☐ *Don't remember*

32. How much of each of the following ALCOHOLIC DRINKS did you drink DURING AN AVERAGE WEEKEND *(Friday to Sunday)?* *(please answer for both time periods, and for each type of drink)*

In the 3 MONTHS BEFORE your last pregnancy	In the FIRST 12 WEEKS of your last pregnancy
0 ☐ Did not drink alcohol at all during these 3 months	0 ☐ Did not drink alcohol at all during the first 12 weeks
DURING AN AVERAGE WEEKEND (Friday-Sunday) I DRANK (IN TOTAL):	DURING AN AVERAGE WEEKEND (Friday-Sunday) I DRANK (IN TOTAL) *(until you stopped, if appropriate)*:
Beer, Lager, Cider ☐☐ pints 9 ☐ *Don't remember*	Beer, Lager, Cider ☐☐ pints 9 ☐ *Don't remember*
Wine ☐☐ glasses 9 ☐ *Don't remember*	Wine ☐☐ glasses 9 ☐ *Don't remember*
Martini, Sherry, Port ☐☐ glasses 9 ☐ *Don't remember*	Martini, Sherry, Port ☐☐ glasses 9 ☐ *Don't remember*
Spirits ☐☐ measures 9 ☐ *Don't remember*	Spirits ☐☐ measures 9 ☐ *Don't remember*
Other alcoholic drinks ☐☐ glasses 9 ☐ *Don't remember*	Other alcoholic drinks ☐☐ glasses 9 ☐ *Don't remember*

33. On average, how often did you SMOKE CIGARETTES in the 3 months before and in the first 12 weeks of your last pregnancy? *(please answer for both time periods)*

If you have NEVER smoked cigarettes please tick here 1 ☐ **and move to *question 34***

In the 3 MONTHS BEFORE your last pregnancy	In the FIRST 12 WEEKS of your last pregnancy
6 ☐ Only smoked occasional cigarette socially	6 ☐ Only smoked occasional cigarette socially
1 ☐ Less than 5 cigarettes per day	1 ☐ Less than 5 cigarettes per day
2 ☐ 5 - 10 cigarettes per day	2 ☐ 5 - 10 cigarettes per day
3 ☐ 11 - 20 cigarettes per day	3 ☐ 11 - 20 cigarettes per day
4 ☐ 21 - 30 cigarettes per day	4 ☐ 21 - 30 cigarettes per day
	5 ☐ Stopped when I found out I was pregnant at ☐☐ weeks
7 ☐ Did not smoke at all during these 3 months	7 ☐ Did not smoke at all during the first 12 weeks
9 ☐ *Don't know / don't remember*	9 ☐ *Don't know / don't remember*

QUESTIONS ABOUT MEDICAL CONDITIONS IN YOUR *LAST PREGNANCY*

34. Did you take *(regularly or for a period of FIVE DAYS or more)* **any tablets, medicines, drugs or other treatment prescribed by a doctor or bought from a chemist, in the 3 months before you became pregnant or in the first 12 weeks of your last pregnancy?** *(please tick all that apply in each time period)*

In the 3 MONTHS BEFORE your last pregnancy	In the FIRST 12 WEEKS of your last pregnancy
0 ☐ No, did not take any medication at this time	0 ☐ No, did not take any medication at this time
YES, I TOOK THE FOLLOWING FOR 5 DAYS OR MORE: **(please tick box and name or describe the medication. If possible say why you took it (more room on back page)):**	YES, I TOOK THE FOLLOWING FOR 5 DAYS OR MORE: **(please tick box and name or describe the medication. If possible say why you took it (more room on back page)):**
1 ☐ Antibiotics *(for infection)*	1 ☐ Antibiotics *(for infection)*
1 ☐ Anti-depressants	1 ☐ Anti-depressants
1 ☐ Antihistamines *(eg for hayfever or itching)*	1 ☐ Antihistamines *(eg for hayfever or itching)*
1 ☐ Asthma treatment (inhaled)	1 ☐ Asthma treatment (inhaled)
1 ☐ Cold or Flu remedies	1 ☐ Cold or Flu remedies
1 ☐ Epilepsy treatment	1 ☐ Epilepsy treatment
1 ☐ Indigestion tablets / medicine	1 ☐ Indigestion tablets / medicine
1 ☐ Insulin for diabetes	1 ☐ Insulin for diabetes
1 ☐ Painkillers *(eg for migraine, arthritis or infection)*	1 ☐ Painkillers *(eg for migraine, arthritis or infection)*
1 ☐ Sleeping pills	1 ☐ Sleeping pills
1 ☐ Steroid cream *(eg for eczema)*	1 ☐ Steroid cream *(eg for eczema)*
1 ☐ Steroid tablets *(eg for arthritis or acute/severe asthma)*	1 ☐ Steroid tablets *(eg for arthritis or acute/severe asthma)*
1 ☐ Travel sickness pills	1 ☐ Travel sickness pills
1 ☐ Treatment for high blood pressure or heart problems	1 ☐ Treatment for high blood pressure or heart problems
1 ☐ Treatment for blood clotting problems *(eg thrombosis)*	1 ☐ Treatment for blood clotting problems *(eg thrombosis)*
1 ☐ Treatment for kidney problems	1 ☐ Treatment for kidney problems
1 ☐ Treatment for thyroid problems	1 ☐ Treatment to prevent miscarriage
1 ☐ Treatment for vaginal thrush	1 ☐ Treatment for thyroid problems
1 ☐ Other *(please give details)*	1 ☐ Treatment for vaginal thrush
	1 ☐ Other *(please give details)*
9 ☐ *Don't know / don't remember*	9 ☐ *Don't know / don't remember*

35. Did you have any X-rays, operations or other medical investigations in the 3 months before you became pregnant or in the first 12 weeks of your last pregnancy? *(please answer for both time periods, and tick more than one if it applies)*

In the 3 MONTHS BEFORE your last pregnancy	In the FIRST 12 WEEKS of your last pregnancy
0 ☐ No, I had no X-rays, operations or other investigations	0 ☐ No, I had no X-rays, operations or other investigations
YES, I HAD THE FOLLOWING:	YES, I HAD THE FOLLOWING:
1 ☐ X-ray - pelvic area (*e.g. fallopian tubes (HSG), hip)*	1 ☐ X-ray - pelvic area (*e.g. fallopian tubes (HSG), hip)*
1 ☐ X-ray - other areas *(e.g. leg, dental x-rays)*	1 ☐ X-ray - other areas *(e.g. leg, dental x-rays)*
1 ☐ Operation under general anaesthetic *(please give details)*	1 ☐ Operation under general anaesthetic *(please give details)*
1 ☐ Other medical investigation *(please give details)*	1 ☐ Other medical investigation *(please give details)*
9 ☐ *Don't know / don't remember*	9 ☐ *Don't know / don't remember*

QUESTIONS ABOUT EMPLOYMENT IN YOUR *LAST PREGNANCY*

36. Were you in paid employment in the 3 months before or in the first 12 weeks of your last pregnancy? *(please answer for both time periods)*

In the 3 MONTHS BEFORE your last pregnancy	In the FIRST 12 WEEKS of your last pregnancy
1 ☐ Yes, full-time	1 ☐ Yes, full-time
2 ☐ Yes, part-time	2 ☐ Yes, part-time
3 ☐ No, looking after family / home *(please go to question 39)*	3 ☐ No, looking after family / home *(please go to question 39)*
4 ☐ No, unemployed *(please go to question 39)*	4 ☐ No, unemployed *(please go to question 39)*
5 ☐ No, student *(please go to question 39)*	5 ☐ No, student *(please go to question 39)*
6 ☐ Other (please specify) _____	6 ☐ Other (please specify) _____
9 ☐ *Don't know / don't remember*	9 ☐ *Don't know / don't remember*

37. If you were in paid employment in the 3 months before or in the first 12 weeks of your last pregnancy, please answer the following? *(please answer for both time periods)*

In the 3 MONTHS BEFORE your last pregnancy	In the FIRST 12 WEEKS of your last pregnancy
a. What was your job title? _____	7 ☐ Exactly the same as in the 3 months before I became pregnant, *please go to* ***question 38 below***
b. What was the nature of business of your employer? *(e.g. factory making clothes, insurance company, school)* _____	**a. What was your job title?** _____
c. What was your role at work?	**b. What was the nature of business of your employer?** *(e.g. factory making clothes, insurance company, school)* _____
1 ☐ Manager	**c. What was your role at work?**
2 ☐ Supervisor	1 ☐ Manager
3 ☐ Employee (other than managerial)	2 ☐ Supervisor
4 ☐ Self employed / freelance *(with no employees)*	3 ☐ Employee (other than managerial)
5 ☐ Self employed *(with 1-9 employees)*	4 ☐ Self employed / freelance *(with no employees)*
6 ☐ Self employed *(with 10+ employees)*	5 ☐ Self employed *(with 1-9 employees)*
7 ☐ Other (please specify) _____	6 ☐ Self employed *(with 10+ employees)*
9 ☐ *Don't know / don't remember*	7 ☐ Other (please specify) _____
d. Did the job involve any of the following? *(please tick all that apply)*	9 ☐ *Don't know / don't remember*
1 ☐ Sitting for more than 6 hours per day	**d. Did the job involve any of the following?** *(please tick all that apply)*
1 ☐ Standing for more than 6 hours per day	1 ☐ Sitting for more than 6 hours per day
1 ☐ Lifting heavy objects or people	1 ☐ Standing for more than 6 hours per day
1 ☐ Exposure to solvents *(e.g. dry cleaning, laboratory work, microelectronics)*	1 ☐ Lifting heavy objects or people
1 ☐ Wearing a 'film badge' to measure radiation exposure	1 ☐ Exposure to solvents *(e.g. dry cleaning, laboratory work, microelectronics)*
0 ☐ None of the above	1 ☐ Wearing a 'film badge' to measure radiation exposure
9 ☐ *Don't know / don't remember*	0 ☐ None of the above
	9 ☐ *Don't know / don't remember*

38. How many weeks pregnant were you when you left work?

☐☐ Weeks
55 ☐ Not applicable *(worked until end of pregnancy)*
66 ☐ Not applicable *(currently pregnant - still working)*
77 ☐ Not applicable *(not in paid employment)*
99 ☐ *Don't know / don't remember*

HOW DID YOU FEEL IN YOUR *LAST PREGNANCY?*

39. How did you feel GENERALLY in the 3 months before and in the first 12 weeks of your last pregnancy? *(please tick all that apply in each time period)*

In the 3 MONTHS BEFORE your last pregnancy	In the FIRST 12 WEEKS of your last pregnancy
1 ☐ Happy	1 ☐ Happy
1 ☐ Relaxed	1 ☐ Relaxed
1 ☐ In control	1 ☐ In control
1 ☐ Stressed or anxious	1 ☐ Stressed or anxious
1 ☐ Very tired (difficult to carry on as normal)	1 ☐ Very tired (difficult to carry on as normal)
1 ☐ Depressed	1 ☐ Depressed
1 ☐ Out of control or overwhelmed	1 ☐ Out of control or overwhelmed
1 ☐ Other (please specify) _____	1 ☐ Other (please specify) _____
9 ☐ *Don't know / don't remember*	9 ☐ *Don't know / don't remember*

40. Did you experience any event which caused you emotional or physical trauma/stress in the 3 months before or in the first 12 weeks of your last pregnancy? *(please tick all that apply in each time period)*

In the 3 MONTHS BEFORE your last pregnancy	In the FIRST 12 WEEKS of your last pregnancy
0 ☐ No, I did not experience any stressful or traumatic event	0 ☐ No, I did not experience any stressful or traumatic event
YES, THE FOLLOWING OCCURRED:	YES, THE FOLLOWING OCCURRED:
1 ☐ Job was generally demanding and/or stressful	1 ☐ Job was generally demanding and/or stressful
1 ☐ Loss or change of job, or job insecurity	1 ☐ Loss or change of job, or job insecurity
1 ☐ Loss of job or job insecurity of husband or partner	1 ☐ Loss of job or job insecurity of husband or partner
1 ☐ Separation or divorce from husband or partner	1 ☐ Separation or divorce from husband or partner
1 ☐ Moving house or major building work	1 ☐ Moving house or major building work
1 ☐ Serious financial problems	1 ☐ Serious financial problems
1 ☐ Accident	1 ☐ Accident
1 ☐ Serious illness	1 ☐ Serious illness
1 ☐ Miscarriage, termination or death of a baby	1 ☐ Serious illness of someone close to you
1 ☐ Serious illness of someone close to you	1 ☐ Death of someone close to you
1 ☐ Death of someone close to you	1 ☐ Other (please specify) _____
1 ☐ Other (please specify) _____	
9 ☐ *Don't know / don't remember*	9 ☐ *Don't know / don't remember*

QUESTIONS ABOUT EXERCISE IN YOUR *LAST PREGNANCY*

41. How often did you do ANY exercise in the 3 months before and in the first 12 weeks of your last pregnancy (include exercise incorporated in your daily life such as walking, climbing stairs, heavy housework etc)? *(please answer for both time periods)*

In the 3 MONTHS BEFORE your last pregnancy	In the FIRST 12 WEEKS of your last pregnancy
1 ☐ Rarely / never	1 ☐ Rarely / never
2 ☐ Once a week	2 ☐ Once a week
3 ☐ 2 - 3 times a week	3 ☐ 2 - 3 times a week
4 ☐ 4 - 6 times a week	4 ☐ 4 - 6 times a week
5 ☐ 6+ times a week	5 ☐ 6+ times a week
9 ☐ *Don't know / don't remember*	9 ☐ *Don't know / don't remember*

QUESTIONS ABOUT YOUR LIFESTYLE IN YOUR *LAST PREGNANCY*

42. How often did you do STRENUOUS exercise in the 3 months before and in the first 12 weeks of your last pregnancy (enough to cause sweating or fast heart beat)? *(please answer for both time periods)*

In the 3 MONTHS BEFORE your last pregnancy	In the FIRST 12 WEEKS of your last pregnancy
1 ☐ Rarely / never	1 ☐ Rarely / never
2 ☐ Once a week	2 ☐ Once a week
3 ☐ 2 - 3 times a week	3 ☐ 2 - 3 times a week
4 ☐ 4 - 6 times a week	4 ☐ 4 - 6 times a week
5 ☐ 6+ times a week	5 ☐ 6+ times a week
9 ☐ *Don't know / don't remember*	9 ☐ *Don't know / don't remember*

43. Did you do any house decorating or were you present when decorating was being done in the 3 months before or in the first 12 weeks of your last pregnancy? *(please tick all that apply in each time period)*

In the 3 MONTHS BEFORE your last pregnancy	In the FIRST 12 WEEKS of your last pregnancy
0 ☐ No, no house decorating was done	0 ☐ No, no house decorating was done
YES, I USED THE FOLLOWING:	YES, I USED THE FOLLOWING:
1 ☐ Ordinary emulsion paint	1 ☐ Ordinary emulsion paint
1 ☐ Low odour emulsion paint (low solvent)	1 ☐ Low odour emulsion paint (low solvent)
1 ☐ Ordinary gloss (clean brushes with white spirit / turps)	1 ☐ Ordinary gloss (clean brushes with white spirit / turps)
1 ☐ Low odour gloss (low solvent, clean brushes with water)	1 ☐ Low odour gloss (low solvent, clean brushes with water)
1 ☐ Paints for metal surfaces (e.g. *Hammerite*)	1 ☐ Paints for metal surfaces (e.g. *Hammerite*)
1 ☐ Glues or other solvents	1 ☐ Glues or other solvents
1 ☐ Creosote or other wood stains	1 ☐ Creosote or other wood stains
1 ☐ Other (please specify)	1 ☐ Other (please specify)
_____	_____
9 ☐ *Don't know / don't remember*	9 ☐ *Don't know / don't remember*

44. Did you have a cat living in, or visiting, your home in the 3 months before and in the first 12 weeks of your last pregnancy? *(please answer for both time periods)*

In the 3 MONTHS BEFORE your last pregnancy	In the FIRST 12 WEEKS of your last pregnancy
0 ☐ No 1 ☐ Yes 9 ☐ *Don't remember*	0 ☐ No 1 ☐ Yes 9 ☐ *Don't remember*
If **YES**, did you come into contact with cat faeces (dirt), for example when handling the litter tray or in the garden?	If **YES**, did you come into contact with cat faeces (dirt), for example when handling the litter tray or in the garden?
1 ☐ Never, *please go to next question*	1 ☐ Never, *please go to next question*
2 ☐ Every day	2 ☐ Every day
3 ☐ 2 - 3 times per week	3 ☐ 2 - 3 times per week
4 ☐ 2 - 3 times per month	4 ☐ 2 - 3 times per month
5 ☐ Less often	5 ☐ Less often
9 ☐ *Don't know / don't remember*	9 ☐ *Don't know / don't remember*
→ **When this happened**, did you wear gloves?	→ **When this happened**, did you wear gloves?
0 ☐ Never 1 ☐ Always 2 ☐ Usually 3 ☐ Sometimes	0 ☐ Never 1 ☐ Always 2 ☐ Usually 3 ☐ Sometimes
9 ☐ *Don't know / don't remember*	9 ☐ *Don't know / don't remember*

MORE QUESTIONS ABOUT YOU IN YOUR *LAST PREGNANCY*

45. The following questions about air travel relate to the FIRST 12 WEEKS of your last pregnancy ONLY

In the FIRST 12 WEEKS of your last pregnancy

a. During the first 12 weeks of your last pregnancy did you travel by aeroplane?

- 1 ☐ Yes
- 2 ☐ No *(please go to question 46)*
- 9 ☐ *Don't remember (please go to question 46)*

b. How many hours IN TOTAL did you spend in the air in the first 12 weeks of your last pregnancy?
(please add the lengths of all flights together - e.g. return to Florida taking 8 hours there and 8 hours back would be 16 hours)

- ☐☐ Total hours
- 999 ☐ *Don't know / don't remember*

c. How many of these return flights were short haul (all domestic (UK) and European flights)**?**

- ☐☐ Number of short haul return flights
- 99 ☐ *Don't know / don't remember*
- 77 ☐ *Not applicable*

d. How many of these return flights were long haul (all other flights)**?**

- ☐☐ Number of long haul return flights
- 99 ☐ *Don't know / don't remember*
- 77 ☐ *Not applicable*

QUESTIONS ABOUT THE FATHER OF YOUR *LAST PREGNANCY*

46. How old was the father of your last pregnancy when the pregnancy ended?

☐☐ years **OR** 99 ☐ *Don't know*

47. How many cigarettes did the father of your last pregnancy smoke, on average per day, in the 3 months before and in the first 12 weeks of your last pregnancy? *(please answer for both time periods)*

In the 3 MONTHS BEFORE your last pregnancy	In the FIRST 12 WEEKS of your last pregnancy
0 ☐ None	0 ☐ None
1 ☐ Less than 5 per day	1 ☐ Less than 5 per day
2 ☐ 5 - 10 per day	2 ☐ 5 - 10 per day
3 ☐ 11 - 20 per day	3 ☐ 11 - 20 per day
4 ☐ 21 - 30 per day	4 ☐ 21 - 30 per day
5 ☐ 30+ per day	5 ☐ 30+ per day
	7 ☐ *Never smoked in my presence*
9 ☐ *Don't know / don't remember*	9 ☐ *Don't know / don't remember*

QUESTIONS ABOUT THE FATHER OF YOUR *LAST PREGNANCY* IN THE *3 MONTHS BEFORE YOU BECAME PREGNANT*

The following questions relate to THE FATHER OF YOUR LAST PREGNANCY and to THE 3 MONTHS BEFORE YOU BECAME PREGNANT ONLY

48. On average, how often did THE FATHER of your last pregnancy drink ALCOHOL in the 3 months BEFORE you became pregnant?

In the 3 MONTHS BEFORE your last pregnancy

- 1 ☐ Every day
- 2 ☐ Three or more days during the week and at weekends
- 3 ☐ Two days or less during the week and at weekends
- 4 ☐ Weekends only
- 5 ☐ Less than once a week
- 6 ☐ Special occasions only
- 0 ☐ Did not drink alcohol at all during these 3 months

- 7 ☐ Has never drunk alcohol (teetotal) *Please go to Question 50*
- 9 ☐ *Don't know / don't remember*

49. How much of each of the following alcoholic drinks did THE FATHER of your last pregnancy drink in an average WEEK in the 3 months BEFORE you conceived?

In the 3 MONTHS BEFORE your last pregnancy

DURING AN AVERAGE WEEK (Monday - Sunday) HE DRANK (IN TOTAL):

Beer, Lager, Cider	☐☐	pints per week	99 ☐ *Don't know /don't remember*
Wine	☐☐	glasses per week	99 ☐ *Don't know /don't remember*
Martini, Sherry, Port	☐☐	glasses per week	99 ☐ *Don't know /don't remember*
Spirits	☐☐	measures per week	99 ☐ *Don't know /don't remember*
Other alcoholic drinks	☐☐	glasses per week	99 ☐ *Don't know /don't remember*

50. Was THE FATHER of your last pregnancy in paid employment at the time you became pregnant?

In the 3 MONTHS BEFORE your last pregnancy

- 1 ☐ Yes, full-time
- 2 ☐ Yes, part-time
- 3 ☐ No, looking after family / home *(please go to question 52)*
- 4 ☐ No, unemployed *(please go to question 52)*
- 5 ☐ No, student *(please go to question 52)*
- 6 ☐ Other (please specify)

_____

- 9 ☐ *Don't know / don't remember*

QUESTIONS ABOUT THE FATHER OF YOUR *LAST PREGNANCY*

51. If THE FATHER of your last pregnancy was in paid employment at the time you became pregnant, please answer the following

In the 3 MONTHS BEFORE your last pregnancy

a. What was his job title?

_____

b. What was the nature of business of his employer? *(e.g. factory making clothes, insurance company, school)*

_____

c. What was his role at work?

1 ☐ Manager
2 ☐ Supervisor
3 ☐ Employee (other than managerial)
4 ☐ Self employed / freelance *(with no employees)*
5 ☐ Self employed *(with 1-9 employees)*
6 ☐ Self employed *(with 10+ employees)*
7 ☐ Other (please specify)

_____

9 ☐ *Don't know / don't remember*

Please skip the following questions if you find them too personal but this is a subject that pregnant women frequently have worries or concerns about, and we need to find out more in order to address these concerns

52.	In the first 3 months (First trimester)	In the second 3 months (Second trimester)	Remainder of pregnancy (Third trimester)
Did you have sex during your LAST pregnancy?	1 ☐ Yes 0 ☐ No 9 ☐ Don't remember	1 ☐ Yes 0 ☐ No 9 ☐ Don't remember 7 ☐ Not applicable	1 ☐ Yes 0 ☐ No 9 ☐ Don't remember 7 ☐ Not applicable
If NO, was this because you ***(please tick all that apply):***	1 ☐ Just did not feel like it and/or were feeling too tired or sick 1 ☐ Were advised not to by a doctor and/or midwife 1 ☐ Were advised not to by a relative or friend 1 ☐ Were worried that it would hurt or cause you to lose the baby 1 ☐ Other reason (please specify) _____	1 ☐ Just did not feel like it and/or were feeling too tired or sick 1 ☐ Were advised not to by a doctor and/or midwife 1 ☐ Were advised not to by a relative or friend 1 ☐ Were worried that it would hurt or cause you to lose the baby 1 ☐ Other reason (please specify) _____ 7 ☐ Not applicable	1 ☐ Just did not feel like it and/or were feeling too tired or sick 1 ☐ Were advised not to by a doctor and/or midwife 1 ☐ Were advised not to by a relative or friend 1 ☐ Were worried that it would hurt or cause you to lose the baby 1 ☐ Other reason (please specify) _____ 7 ☐ Not applicable
If YES, did you ever bleed after having sex?	1 ☐ Yes 0 ☐ No 9 ☐ Don't remember 7 ☐ Not applicable	1 ☐ Yes 0 ☐ No 9 ☐ Don't remember 7 ☐ Not applicable	1 ☐ Yes 0 ☐ No 9 ☐ Don't remember 7 ☐ Not applicable

MORE QUESTIONS ABOUT YOUR *LAST PREGNANCY*

53. Is there anything else (good or bad) that you or the father of the pregnancy experienced or were exposed to that you feel may have affected your last pregnancy?

1 ☐ Yes 0 ☐ No 9 ☐ *Don't remember*

If YES, please give details below:

QUESTIONS ABOUT PREGNANCY LOSS

54. If your last pregnancy ended in a miscarriage, please could you tell us:

a. Were you seen by a doctor? 1 ☐ Yes 0 ☐ No 9 ☐ *Don't remember*

b. Did you go to hospital? 1 ☐ Yes 0 ☐ No 9 ☐ *Don't remember*

If YES, which department/s were you seen by? *(please tick all that apply)*

1 ☐ Accident & Emergency (Casualty)
1 ☐ Early Pregnancy Unit
1 ☐ Gynaecological Ward
1 ☐ Labour Ward
1 ☐ Other (please specify) _____
9 ☐ *Don't know / don't remember*

c. Were you given an operation? 1 ☐ Yes 0 ☐ No 9 ☐ *Don't remember*

If YES, please give details: _____

d. Were you given any tablets or drugs? 1 ☐ Yes 0 ☐ No 9 ☐ *Don't remember*

If YES, please give details: _____

e. Did you have any investigations to find out what might have caused you to lose the baby?

1 ☐ Yes 0 ☐ No 9 ☐ *Don't remember*

If YES, please give brief details: _____

f. Were you told why you might have lost the baby?

1 ☐ Yes 0 ☐ No 9 ☐ *Don't remember*

If YES, please give brief details: _____

g. What advice were you given about how long to wait before trying for another baby?

1 ☐ Try again straight away 2 ☐ Wait 1-2 months 3 ☐ Wait 3 - 5 months
4 ☐ Wait 6 - 12 months 5 ☐ Wait a year or more 7 ☐ No advice given 9 ☐ *Don't remember*

h. Were you given any professional support to help you to cope with the loss of your baby?

1 ☐ Yes 0 ☐ No, no support offered 2 ☐ Support offered, but didn't want it 9 ☐ *Don't remember*

If YES, please give brief details: _____

PERMISSION TO CONSULT MEDICAL NOTES

In order that our study results are based on as detailed and accurate data as possible, please may we have permission to consult your medical records about the medical information you have given us in this questionnaire relating to pregnancy and fertility, if necessary? This would involve writing to your GP and/or hospital to confirm medical details. Please tick the box and fill in your details, if you agree to this.

1 ☐ I give permission for my medical records to be examined for confidential use in The National Women's Health Study

FULL NAME _____

SURNAME AT BIRTH _____

ALL PREVIOUS NAMES (if applicable) _____

SIGNATURE _____ **DATE** _____

GP DETAILS

Please could you tell us the name and address of your current GP:

NAME OF GP _____

ADDRESS OF GP _____

_____

_____

POSTCODE ☐☐☐☐ ☐☐☐

TELEPHONE NO. OF GP _____

THIS SECTION ASKS ABOUT YOUR CONTACT DETAILS

It would be helpful to know the best way of contacting you again, if we need to. This would only be relating to the information you have told us about on this questionnaire, for example to resolve queries. Please indicate in the box below if you would be willing for us to contact you again in the future:

1 ☐ Yes, I am willing to be contacted again

0 ☐ Please do not contact me again

If you have answered YES and are prepared to be contacted again, we would be grateful if you could indicate in the box below a preferred contact address, telephone number and the time when you can be contacted:

Same as on front of questionnaire? 1 ☐ Yes 0 ☐ No, *please give other preferred address below*

Other preferred address _____

_____

_____

Postcode ☐☐☐☐ ☐☐☐

Daytime telephone number _____

Evening telephone number _____

Preferred contact time ☐ Daytime am ☐ Daytime pm ☐ Evening ☐ Anytime

ADDITIONAL COMMENTS

If there is anything else you would like to add, please tell us here:

THANK YOU VERY MUCH FOR YOUR HELP WITH THIS SURVEY

Please make sure you have answered all the questions and kindly return the completed form in the enclosed prepaid envelope to:

DR NOREEN MACONOCHIE
THE NATIONAL WOMEN'S HEALTH STUDY
EPIDEMIOLOGY UNIT
DEPARTMENT OF EPIDEMIOLOGY AND POPULATION HEALTH
LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE
KEPPEL STREET
LONDON
WC1E 7HT

This study has been funded by

COMMUNITY FUND
Lottery money making a difference

FREEPHONE HELPLINE: 0800 068 3875

A.2.2 SUPPLEMENTARY INFORMATION ON EXCLUSIONS

Women excluded from analysis using self-reported infertility as outcome measure

Forty-four women reported that they had experienced problems trying to get pregnant at some point during their reproductive life, but did not give the date (or approximate date) that these problems first occurred. All 44 women were therefore excluded from the analysis using self-reported infertility as the outcome measure, as it was not possible to work out at which point of their reproductive career this infertility occurred. These women represented a total of 145 pregnancy attempts, 44 of which were unsuccessful attempts at conception and 101 which ended in a conception. Some characteristics of these women and their pregnancy attempts are included below.

Table A.2.1: Age at survey of 44 women excluded due to missing information on timing of first infertility

Age at survey	n	(%)
<30	6	(13.6)
30-34	8	(18.2)
35-39	6	(13.6)
40-44	13	(29.5)
45-49	5	(11.4)
≥50	6	(13.6)

Table A.2.2: Characteristics of 44 women excluded due to missing information on timing of first infertility

	Yes		No	
	n	(%)	No	(%)
Ever pregnant	37	(84.1)	7	(15.9)
Ever livebirth	32	(72.7)	12	(17.3)

On the following pages is a list of all 101 pregnancies occurring to these women, and specific details of these pregnancies.

ID no.	pregnancy order	date at end of pregnancy	age at end of pregnancy	pregnancy outcome	birthweight	gestation	pregnancy planned?	time to pregnancy (if planned)	multiple birth?
1637	1	25-Jun-1993	44-49	live birth	normal birthweight	term	missing	.	singleton
1695	1	8-Sep-1988	40-44	live birth	normal birthweight	term	planned	3 - <6 months	singleton
1695	2	11-Jul-1990	40-44	live birth	normal birthweight	term	planned	3 - <6 months	singleton
1695	3	27-Apr-1996	40-44	live birth	normal birthweight	term	unplanned	.	singleton
1695	4	17-Jul-1999	40-44	live birth	normal birthweight	term	unplanned	.	singleton
4748	1	2-Sep-1989	44-49	live birth	low birthweight	preterm	unplanned	.	singleton
4748	2	7-Oct-1992	44-49	live birth	normal birthweight	term	unplanned	.	singleton
8286	1	17-Jul-1996	30-34	live birth	normal birthweight	term	planned	3 - <6 months	singleton
8286	2	10-Jun-1999	30-34	live birth	normal birthweight	term	planned	6 - <12 months	singleton
9667	1	15-Jan-1977	50+	miscarriage	.	.	planned	12mths+	singleton
9667	2	27-Feb-1978	50+	live birth	normal birthweight	term	planned	6 - <12 months	singleton
9667	3	15-Jul-1982	50+	miscarriage	.	.	planned	12mths+	singleton
12260	1	16-May-1987	40-44	live birth	normal birthweight	term	planned	3 - <6 months	singleton
12260	2	16-May-1990	40-44	live birth	normal birthweight	term	planned	3 - <6 months	singleton
12260	3	21-Jan-2000	40-44	miscarriage	.	.	planned	6 - <12 months	singleton
12260	4	5-Oct-2001	40-44	live birth	normal birthweight	term	planned	3 - <6 months	singleton
12405	1	11-Mar-1983	44-49	live birth	normal birthweight	term	planned	12mths+	singleton
12405	2	30-Jun-1988	44-49	ectopic	.	.	planned	12mths+	singleton
12405	3	30-Jun-1989	44-49	miscarriage	.	.	missing	.	singleton
12405	4	1-Aug-1990	44-49	live birth	normal birthweight	term	planned	missing	singleton
12405	5	29-Aug-1991	44-49	live birth	normal birthweight	term	unplanned	.	singleton
12405	6	30-Jun-1996	44-49	miscarriage	.	.	unplanned	.	singleton

ID no.	pregnancy order	date at end of pregnancy	age at end of pregnancy	pregnancy outcome	birthweight	gestation	pregnancy planned?	time to pregnancy (if planned)	multiple birth?
13200	1	6-Aug-1985	40-44	live birth	normal birthweight	term	planned	12mths+	singleton
13200	2	2-May-1994	40-44	live birth	normal birthweight	preterm	planned	<3 months	singleton
13200	3	5-Jul-1995	40-44	live birth	normal birthweight	term	unplanned	.	singleton
13200	4	11-Sep-2002	40-44	ongoing	.	.	planned	12mths+	singleton
14562	1	13-May-1999	<30	miscarriage	.	.	unplanned	.	singleton
15083	1	15-May-1975	50+	miscarriage	.	.	unplanned	.	singleton
15083	2	1-Oct-1976	50+	live birth	normal birthweight	term	planned	3 - <6 months	singleton
15083	3	2-Jan-1979	50+	live birth	normal birthweight	term	planned	<3 months	singleton
15083	4	13-Aug-1980	50+	live birth	normal birthweight	term	planned	6 - <12 months	singleton
15083	5	8-Mar-1982	50+	live birth	normal birthweight	term	planned	6 - <12 months	singleton
19130	1	17-Nov-1991	40-44	live birth	normal birthweight	term	planned	12mths+	singleton
19130	2	6-Aug-1993	40-44	live birth	normal birthweight	term	unplanned	.	singleton
19373	1	24-Jul-1997	30-34	live birth	normal birthweight	term	planned	6 - <12 months	singleton
19373	2	8-Dec-1999	30-34	live birth	normal birthweight	term	planned	<3 months	singleton
22525	1	30-Jun-1984	44-49	miscarriage	.	.	planned	6 - <12 months	singleton
22525	2	18-Jan-1986	44-49	live birth	normal birthweight	term	planned	12mths+	singleton
22525	3	13-Aug-1990	44-49	termination (clin)	.	.	planned	missing	singleton
22525	4	15-Feb-1993	44-49	miscarriage	.	.	planned	missing	singleton
22525	5	7-Apr-1997	44-49	live birth	normal birthweight	preterm	missing	.	singleton
23041	1	15-Jan-1975	44-49	live birth	.	term	planned	12mths+	singleton
23041	2	20-Jan-1986	44-49	live birth	.	term	planned	12mths+	singleton

ID no.	pregnancy order	date at end of pregnancy	age at end of pregnancy	pregnancy outcome	birthweight	gestation	pregnancy planned?	time to pregnancy (if planned)	multiple birth?
24378	1	15-Jun-1980	50+	miscarriage	.	.	planned	12mths+	singleton
24378	2	3-Jul-1981	50+	live birth	normal birthweight	term	planned	12mths+	singleton
24378	3	30-Jun-1984	50+	miscarriage	.	.	planned	12mths+	multiple
24378	4	16-Jul-1986	50+	live birth	normal birthweight	term	planned	12mths+	singleton
24786	1	2-Jul-1995	30-34	live birth	normal birthweight	term	planned	<3 months	singleton
27167	1	22-Jul-1991	30-34	live birth	normal birthweight	term	unplanned	.	singleton
27348	1	30-Jun-1982	40-44	termination (non-clin)	.	.	unplanned	.	singleton
27348	2	15-Feb-2001	40-44	miscarriage	.	.	planned	<3 months	singleton
31311	1	17-Dec-1985	44-49	live birth	normal birthweight	preterm	planned	12mths+	singleton
31311	2	6-Apr-1987	44-49	live birth	normal birthweight	term	planned	<3 months	singleton
31380	1	30-Jun-1973	50+	termination (non-clin)	.	.	unplanned	.	singleton
31380	2	2-Sep-1980	50+	live birth	normal birthweight	term	planned	missing	singleton
31380	3	30-Dec-1983	50+	live birth	normal birthweight	term	planned	missing	singleton
31380	4	30-Dec-1991	50+	miscarriage	.	.	unplanned	.	singleton
35421	1	12-Aug-1990	35-39	live birth	normal birthweight	term	planned	12mths+	singleton
35421	2	7-May-1998	35-39	live birth	normal birthweight	term	planned	12mths+	singleton
35421	3	10-Apr-2000	35-39	live birth	.	term	planned	3 - <6 months	multiple
38036	1	20-Dec-1986	40-44	live birth	normal birthweight	term	planned	12mths+	singleton
38036	2	25-Oct-1988	40-44	live birth	.	term	planned	missing	singleton
38289	1	25-Oct-1995	40-44	live birth	normal birthweight	term	planned	12mths+	singleton

ID no.	pregnancy order	date at end of pregnancy	age at end of pregnancy	pregnancy outcome	birthweight	gestation	pregnancy planned?	time to pregnancy (if planned)	multiple birth?
38289	2	9-Dec-1996	40-44	live birth	normal birthweight	term	planned	3 - <6 months	singleton
43794	1	21-May-1986	40-44	live birth	normal birthweight	term	planned	missing	singleton
43794	2	22-Dec-1988	40-44	live birth	normal birthweight	term	planned	missing	singleton
43794	3	23-Aug-1993	40-44	live birth	normal birthweight	term	planned	missing	singleton
45013	1	30-Dec-1982	50+	live birth	normal birthweight	term	planned	12mths+	singleton
45013	2	25-Feb-1988	50+	live birth	normal birthweight	term	planned	12mths+	singleton
48804	1	15-Jun-1996	<30	termination (non-clin)	.	.	unplanned	.	singleton
48804	2	30-Jun-1997	<30	termination (non-clin)	.	.	unplanned	.	singleton
48804	3	30-Apr-2001	<30	miscarriage	.	.	unplanned	.	singleton
49711	1	1-Mar-1989	30-34	live birth	normal birthweight	term	unplanned	.	singleton
49711	2	20-Feb-1992	30-34	live birth	normal birthweight	term	unplanned	.	singleton
49711	3	11-Jul-1998	30-34	live birth	normal birthweight	preterm	planned	12mths+	singleton
49711	4	24-Jun-2002	30-34	ongoing	.	.	planned	12mths+	singleton
50520	1	15-May-1994	44-49	miscarriage	.	.	planned	12mths+	singleton
51542	1	23-Feb-1988	50+	live birth	normal birthweight	term	missing	.	singleton
52182	1	31-Jan-1998	35-39	live birth	normal birthweight	term	unplanned	.	singleton
54698	1	21-Sep-1996	<30	live birth	normal birthweight	term	planned	<3 months	singleton
54698	2	15-Apr-1999	<30	miscarriage	.	.	unplanned	.	singleton
54698	3	10-May-2002	<30	ongoing	.	.	planned	12mths+	singleton
55917	1	15-Feb-1970	50+	miscarriage	.	.	unplanned	.	singleton

ID no.	pregnancy order	date at end of pregnancy	age at end of pregnancy	pregnancy outcome	birthweight	gestation	pregnancy planned?	time to pregnancy (if planned)	multiple birth?
55917	2	6-Dec-1973	50+	live birth	normal birthweight	term	unplanned		singleton
55917	3	6-Jul-1978	50+	live birth	normal birthweight	term	planned	12mths+	singleton
56810	1	15-Dec-2001	35-39	miscarriage	.	.	planned	6 - <12 months	singleton
57373	1	2-Aug-1998	35-39	miscarriage	.	.	planned	12mths+	singleton
57373	2	29-Jul-1999	35-39	live birth	normal birthweight	term	planned	3 - <6 months	singleton
57860	1	15-May-1988	40-44	miscarriage	.	.	planned	3 - <6 months	singleton
57860	2	15-Feb-1989	40-44	molar pregnancy	.	.	planned	3 - <6 months	singleton
57860	3	15-Sep-1991	40-44	miscarriage	.	.	planned	3 - <6 months	singleton
57860	4	15-Jan-1992	40-44	miscarriage	.	.	planned	3 - <6 months	singleton
57860	5	17-May-1994	40-44	live birth	normal birthweight	term	planned	12mths+	singleton
57860	6	19-Mar-1996	40-44	live birth	normal birthweight	term	planned	3 - <6 months	singleton
60465	1	15-Aug-1995	30-34	live birth	normal birthweight	term	unplanned	.	singleton
60465	2	12-Aug-1999	30-34	live birth	normal birthweight	term	planned	12mths+	singleton
70043	1	3-Nov-1996	35-39	live birth	normal birthweight	term	planned	12mths+	singleton
70043	2	12-Apr-1998	35-39	miscarriage	.	.	missing	.	singleton
70043	3	26-Jun-1998	35-39	miscarriage	.	.	planned	<3 months	singleton
70043	4	26-Feb-1999	35-39	miscarriage	.	.	planned	6 - <12 months	singleton
70043	5	19-Jan-2000	35-39	miscarriage	.	.	planned	6 - <12 months	singleton

A.2.3 SUPPLEMENTARY TABLES

Additional tables for analysis of past adverse outcomes and self-reported secondary infertility

Table A.2.3: Odds ratios for the association between past adverse outcomes and self-reported secondary infertility, adjusted for potential confounding variables

		crude OR (95% CI)	Adjusted for age OR (95% CI)	Adjusted for year of pregnancy OR (95% CI)	Adjusted for no. of previous pregnancy attempts OR (95% CI)	Adjusted for age and year of pregnancy OR (95% CI)	Adjusted for age and year of pregnancy & no. of previous pregnancy attempts OR (95% CI)
TERMINATION							
In any past pregnancy	Yes	2.32 (1.79, 3.00)	2.24 (1.73, 2.91)	2.10 (1.62, 2.73)	2.55 (1.97, 3.30)	2.08 (1.60, 2.70)	2.35 (1.81, 3.06)
In last pregnancy	Yes	3.00 (2.25, 4.00)	3.04 (2.27, 4.08)	2.79 (2.08, 3.73)	2.87 (2.14, 3.83)	2.81 (2.09, 3.78)	2.63 (1.95, 3.54)
CLINICALLY INDICATED TERMINATIONS							
In any past pregnancy	*Yes*	*2.45 (1.21, 4.93)*	*2.28 (1.17, 4.66)*	*2.26 (1.11, 4.59)*	*2.70 (1.34, 5.45)*	*2.17 (1.06, 4.45)*	*2.46 (1.19, 5.08)*
In last pregnancy	*Yes*	*2.44 (1.03, 5.74)*	*2.28 (0.96, 5.40)*	*2.26 (0.96, 5.31)*	*2.51 (1.06, 5.95)*	*2.17 (0.92, 5.12)*	*2.24 (0.93, 5.37)*
NON-CLINICALLY INDICATED TERMINATIONS							
In any past pregnancy	*Yes*	*2.25 (1.72, 2.94)*	*2.18 (1.67, 2.85)*	*2.04 (1.56, 2.67)*	*2.46 (1.88, 3.22)*	*2.02 (1.54, 2.65)*	*2.28 (1.74, 3.00)*
In last pregnancy	*Yes*	*3.01 (2.23, 4.06)*	*3.08 (2.27, 4.18)*	*2.80 (2.07, 3.79)*	*2.85 (2.11, 3.86)*	*2.84 (2.08, 3.87)*	*2.62 (1.92, 3.58)*
MISCARRIAGE							
In any past pregnancy	Yes	1.35 (1.08, 1.69)	1.28 (1.02, 1.61)	1.24 (0.98, 1.56)	1.76 (1.36, 2.27)	1.22 (0.96, 1.53)	1.71 (1.32, 2.21)
In last pregnancy	Yes	1.52 (1.18, 1.94)	1.47 (1.14, 1.88)	1.39 (1.08, 1.79)	1.70 (1.31, 2.20)	1.37 (1.07, 1.77)	1.61 (1.24, 2.10)
1st TRIMESTER MISCARRIAGE							
In any past pregnancy	*Yes*	*1.42 (1.12, 1.81)*	*1.35 (1.06, 1.72)*	*1.28 (1.00, 1.63)*	*1.82 (1.40, 2.38)*	*1.26 (0.99, 1.61)*	*1.74 (1.32, 2.28)*
In last pregnancy	*Yes*	*1.65 (1.27, 2.15)*	*1.60 (1.22, 2.08)*	*1.49 (1.14, 1.95)*	*1.84 (1.40, 2.41)*	*1.48 (1.13, 1.93)*	*1.72 (1.20, 2.27)*
2nd TRIMESTER MISCARRIAGE							
In any past pregnancy	*Yes*	*0.86 (0.54, 1.37)*	*0.83 (0.52, 1.32)*	*0.84 (0.53, 1.35)*	*1.02 (0.63, 1.66)*	*0.83 (0.52, 1.33)*	*1.08 (0.66, 1.76)*
In last pregnancy	*Yes*	*0.93 (0.52, 1.68)*	*0.91 (0.50, 1.65)*	*0.94 (0.52, 1.69)*	*1.02 (0.57, 1.86)*	*0.92 (0.51, 1.67)*	*1.05 (0.58, 1.91)*
STILLBIRTH							
In any past pregnancy	Yes	0.88 (0.42, 1.88)	0.89 (0.42, 1.90)	1.04 (0.47, 2.56)	1.01 (0.47, 2.16)	1.03 (0.47, 2.23)	1.31 (0.60, 2.86)
In last pregnancy	Yes	1.03 (0.37, 2.84)	1.07 (0.39, 2.98)	1.27 (0.46, 3.55)	1.05 (0.38, 2.88)	1.26 (0.45, 3.53)	1.35 (0.49, 3.78)
ECTOPIC PREGNANCY							
In any past pregnancy	Yes	3.70 (2.02, 6.78)	3.56 (1.90, 6.66)	3.38 (1.77, 6.45)	4.43 (2.41, 8.14)	3.37 (1.75, 6.48)	4.35 (2.26, 8.40)
In last pregnancy	Yes	4.81 (2.47, 9.38)	4.93 (2.51, 9.67)	4.61 (2.29, 9.27)	5.30 (2.71, 10.39)	4.76 (2.38, 9.53)	5.47 (2.70, 11.1)
LOW BIRTHWEIGHT							
In any past pregnancy	Yes	0.78 (0.51, 1.21)	0.78 (0.50, 1.21)	0.81 (0.52, 1.25)	0.83 (0.54, 1.28)	0.81 (0.52, 1.25)	0.89 (0.57, 1.37)
In last pregnancy	Yes	0.76 (0.44, 1.31)	0.78 (0.45, 1.35)	0.79 (0.46, 1.37)	0.74 (0.43, 1.27)	0.80 (0.46, 1.38)	0.77 (0.44, 1.33)
PRETERM DELIVERY							
In any past pregnancy	Yes	1.04 (0.70, 1.53)	1.01 (0.68, 1.49)	1.01 (0.68, 1.49)	1.12 (0.76, 1.64)	1.00 (0.67, 1.48)	1.10 (0.75, 1.64)
In last pregnancy	Yes	0.89 (0.54, 1.45)	0.89 (0.54, 1.47)	0.87 (0.53, 1.43)	0.88 (0.53, 1.44)	0.88 (0.53, 1.45)	0.86 (0.52, 1.43)

N.B. greyed out cells highlight odds ratios significant at $p<0.05$

Table A.2.4: Odds ratios for the association between past adverse outcomes and self-reported secondary infertility, adjusted for potential confounding variables including previous ectopic pregnancy

		crude	Adjusted for age and year of pregnancy	Adjusted for age and year of pregnancy & no. of previous pregnancy attempts	Adjusted for age and year of pregnancy and previous ectopic	Adjusted for age and year of pregnancy & no. of previous pregnancy attempts and previous ectopic
		OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
TERMINATION						
In any past pregnancy	Yes	2.32 (1.79, 3.00)	2.08 (1.60, 2.70)	2.35 (1.81, 3.06)	2.12 (1.63, 2.76)	2.44 (1.87, 3.18)
In last pregnancy	Yes	3.00 (2.25, 4.00)	2.81 (2.09, 3.78)	2.63 (1.95, 3.54)	2.90 (2.15, 3.90)	2.70 (2.00, 3.65)
CLINICALLY INDICATED TERMINATIONS						
In any past pregnancy	*Yes*	*2.45 (1.21, 4.93)*	*2.17 (1.06, 4.45)*	*2.46 (1.19, 5.08)*	*2.23 (1.09, 4.57)*	2.57 (1.24, 5.31)
In last pregnancy	*Yes*	*2.44 (1.03, 5.74)*	*2.17 (0.92, 5.12)*	*2.24 (0.93, 5.37)*	*2.22 (0.94, 5.25)*	2.31 (0.96, 5.55)
NON-CLINICALLY INDICATED TERMINATIONS						
In any past pregnancy	*Yes*	*2.25 (1.72, 2.94)*	*2.02 (1.54, 2.65)*	*2.28 (1.74, 3.00)*	*2.06 (1.57, 2.71)*	2.36 (1.80, 3.11)
In last pregnancy	*Yes*	*3.01 (2.23, 4.06)*	*2.84 (2.08, 3.87)*	*2.62 (1.92, 3.58)*	*2.92 (2.14, 3.99)*	2.69 (1.97, 3.68)
MISCARRIAGE						
In any past pregnancy	Yes	1.35 (1.08, 1.69)	1.22 (0.96, 1.53)	1.71 (1.32, 2.21)	1.21 (0.96, 1.52)	1.74 (1.34, 2.26)
In last pregnancy	Yes	1.52 (1.18, 1.94)	1.37 (1.07, 1.77)	1.61 (1.24, 2.10)	1.39 (1.07, 1..79)	1.65 (1.27, 2.16)
1st TRIMESTER MISCARRIAGE						
In any past pregnancy	*Yes*	*1.42 (1.12, 1.81)*	*1.26 (0.99, 1.61)*	*1.74 (1.32, 2.28)*	*1.25 (0.97, 1.60)*	1.77 (1.34, 2.32)
In last pregnancy	*Yes*	*1.65 (1.27, 2.15)*	*1.48 (1.13, 1.93)*	*1.72 (1.20, 2.27)*	*1.49 (1.13, 1.96)*	1.77 (1.34, 2.33)
2nd TRIMESTER MISCARRIAGE						
In any past pregnancy	*Yes*	*0.86 (0.54, 1.37)*	*0.83 (0.52, 1.33)*	*1.08 (0.66, 1.76)*	*0.81 (0.50, 1.31)*	1.08 (0.66, 1.77)
In last pregnancy	*Yes*	*0.93 (0.52, 1.68)*	*0.92 (0.51, 1.67)*	*1.05 (0.58, 1.91)*	*0.91 (0.50, 1.66)*	1.06 (0.58, 1.93)
STILLBIRTH						
In any past pregnancy	Yes	0.88 (0.42, 1.88)	1.03 (0.47, 2.23)	1.31 (0.60, 2.86)	1.04 (0.48, 2.26)	1.37 (0,63, 2.97)
In last pregnancy	Yes	1.03 (0.37, 2.84)	1.26 (0.45, 3.53)	1.35 (0.49, 3.78)	1.26 (0.45, 3.53)	1.38 (0.49, 3.84)
LOW BIRTHWEIGHT						
In any past pregnancy	Yes	3.70 (2.02, 6.78)	0.81 (0.52, 1.25)	0.89 (0.57, 1.37)	0.81 (0.52, 1.26)	0.90 (0.58, 1.40)
In last pregnancy	Yes	4.81 (2.47, 9.38)	0.80 (0.46, 1.38)	0.77 (0.44, 1.33)	0.82 (0.47, 1.41)	0.79 (0.45, 1.36)
PRETERM DELIVERY						
In any past pregnancy	Yes	0.78 (0.51, 1.21)	1.00 (0.67, 1.48)	1.10 (0.75, 1.64)	0.99 (0.66, 1.47)	1.11 (0.75, 1.65)
In last pregnancy	Yes	0.76 (0.44, 1.31)	0.88 (0.53, 1.45)	0.86 (0.52, 1.43)	0.89 (0.54, 1.47)	0.88 (0.53, 1.46)

N.B. greyed out cells highlight odds ratios significant at $p<0.05$

Additional tables for analysis of past adverse outcomes and secondary infertility defined as TTP ≥ 12 months

Table A.2.5: Odds ratios for the association between past adverse outcomes and secondary infertility defined as TTP ≥ 12 months, adjusted for potential confounding variables

		crude OR (95% CI)	Adjusted for age OR (95% CI)	Adjusted for year of pregnancy OR (95% CI)	Adjusted for no. of previous pregnancies OR (95% CI)	Adjusted for age and year of pregnancy OR (95% CI)	Adjusted for age and year of pregnancy & no. of previous pregnancies OR (95% CI)
TERMINATION							
In any past pregnancy	Yes	1.17 (0.83, 1.65)	1.14 (0.81, 1.60)	1.16 (0.82, 1.63)	1.14 (0.80, 1.61)	1.15 (0.82, 1.63)	1.16 (0.82, 1.64)
In last pregnancy	Yes	1.07 (0.72, 1.61)	1.09 (0.72, 1.63)	1.07 (0.71, 1.60)	1.12 (0.73, 1.66)	1.09 (0.73, 1.64)	1.12 (0.74, 1.68)
CLINICALLY INDICATED TERMINATIONS							
In any past pregnancy	*Yes*	*2.38 (1.12, 5.07)*	*2.28 (1.06, 4.87)*	*2.36 (1.10, 5.03)*	*2.34 (1.11, 4.96)*	*2.31 (1.07, 4.98)*	*2.38 (1.10, 5.12)*
In last pregnancy	*Yes*	*1.65 (0.69, 3.92)*	*1.60 (0.66, 3.87)*	*1.62 (0.68, 3.84)*	*1.61 (0.67, 3.89)*	*1.62 (0.68, 3.86)*	*1.62 (0.67, 3.91)*
NON-CLINICALLY INDICATED TERMINATIONS							
In any past pregnancy	*Yes*	*1.00 (0.69, 1.46)*	*0.98 (0.68, 1.42)*	*0.99 (0.68, 1.44)*	*0.97 (0.67,1.42)*	*0.99 (0.68, 1.44)*	*0.99 (0.68, 1.45)*
In last pregnancy	*Yes*	*0.97 (0.62, 1.53)*	*0.99 (0.63, 1.56)*	*0.97 (0.62, 1.53)*	*1.01 (0.64, 1.60)*	*1.00 (0.63, 1.57)*	*1.02 (0.65, 1.62)*
MISCARRIAGE							
In any past pregnancy	Yes	1.25 (1.02, 1.53)	1.20 (0.98, 1.48)	1.25 (1.02, 1.53)	1.26 (0.99, 1.60)	1.21 (0.98, 1.49)	1.29 (1.01, 1.64)
In last pregnancy	Yes	1.22 (0.99, 1.51)	1.18 (0.95, 1.47)	1.21 (0.97, 1.51)	1.19 (0.95, 1.49)	1.21 (0.96, 1.52)	1.22 (0.97, 1.54)
1st TRIMESTER MISCARRIAGE							
In any past pregnancy	*Yes*	*1.28 (1.03, 1.59)*	*1.22 (0.98, 1.52)*	*1.28 (1.02, 1.59)*	*1.29 (1.01, 1.65)*	*1.24 (0.99, 1.54)*	*1.32 (1.03, 1.68)*
In last pregnancy	*Yes*	*1.21 (0.95, 1.53)*	*1.17 (0.92, 1.49)*	*1.20 (0.94, 1.53)*	*1.18 (0.92, 1.50)*	*1.19 (0.94, 1.53)*	*1.21 (0.94, 1.55)*
2nd TRIMESTER MISCARRIAGE							
In any past pregnancy	*Yes*	*0.98 (0.66, 1.44)*	*0.96 (0.64, 1.43)*	*0.98 (0.66, 1.44)*	*0.94 (0.62, 1.42)*	*0.96 (0.65, 1.42)*	*0.98 (0.65, 1.47)*
In last pregnancy	*Yes*	*1.16 (0.75, 1.80)*	*1.16 (0.75, 1.80)*	*1.17 (0.76, 1.80)*	*1.16 (0.75, 1.79)*	*1.14 (0.74, 1.78)*	*1.17 (0.75, 1.82)*
STILLBIRTH							
In any past pregnancy	Yes	1.71 (0.90, 3.23)	1.75 (0.92, 3.33)	1.80 (0.95, 3.40)	1.68 (0.88, 3.21)	1.75 (0.94, 3.37)	1.82 (0.96, 3.48)
In last pregnancy	Yes	1.76 (0.90, 3.44)	1.83 (0.92, 3.61)	1.87 (0.95, 3.67)	1.84 (0.93, 3. 64)	1.74 (0.89, 3.42)	1.84 (0.93, 3.64)
ECTOPIC PREGNANCY							
In any past pregnancy	Yes	3.84 (2.30, 6.40)	3.70 (2.23, 6.13)	3.78 (2.27, 6.30)	3.80 (2.26, 6.40)	3.72 (2.26, 6.14)	3.83 (2.30, 6.38)
In last pregnancy	Yes	3.71 (2.04, 6.73)	3.73 (2.06, 6.76)	3.63 (2.00, 6.59)	3.74 (2.07, 6.76)	3.65 (2.00, 6.64)	3.73 (2.06, 6.79)
LOW BIRTHWEIGHT							
In any past pregnancy	Yes	1.14 (0.79, 1.65)	1.15 (0.80, 1.66)	1.14 (0.79, 1.65)	1.14 (0.78, 1.66)	1.13 (0.79, 1.64)	1.16 (0.80, 1.68)
In last pregnancy	Yes	1.44 (0.96, 2.17)	1.47 (0.98, 2.21)	1.44 (0.96, 2.17)	1.45 (0.96, 2.17)	1.46 (0.97, 2.19)	1.45 (0.97, 2.17)
PRETERM DELIVERY							
In any past pregnancy	Yes	1.41 (1.00, 1.98)	1.39 (0.99, 1.96)	1.40 (1.00, 1.97)	1.40 (1.00, 1.98)	1.39 (0.99, 1.95)	1.42 (1.01, 2.00)
In last pregnancy	Yes	1.70 (1.16, 2.47)	1.72 (1.18, 2.51)	1.69 (1.16, 2.46)	1.71 (1.17, 2.49)	1.71 (1.18, 2.50)	1.72 (1.18, 2.50)

N.B. greyed out cells highlight odds ratios significant at $p<0.05$

Table A.2.6: Odds ratios for the association between past adverse outcomes and secondary infertility defined as TTP ≥ 12 months, adjusted for potential confounding variables including previous ectopic pregnancy

		crude OR (95% CI)	Adjusted for age and year of pregnancy OR (95% CI)	Adjusted for age and year of pregnancy & no. of previous pregnancies OR (95% CI)	Adjusted for age and year of pregnancy and previous ectopic OR (95% CI)	Adjusted for age and year of pregnancy & no. of previous pregnancies and previous ectopic OR (95% CI)
TERMINATION						
In any past pregnancy	Yes	1.17 (0.83, 1.65)	1.15 (0.82, 1.63)	1.16 (0.82, 1.64)	1.19 (0.84, 1.68)	1.22 (0.86, 1.72)
In last pregnancy	Yes	1.07 (0.72, 1.61)	1.09 (0.73, 1.64)	1.12 (0.74, 1.68)	1.15 (0.76, 1.72)	1.16 (0.77, 1.74)
CLINICALLY INDICATED TERMINATIONS						
In any past pregnancy	*Yes*	*2.38 (1.12, 5.07)*	*2.31 (1.07, 4.98)*	*2.38 (1.10, 5.12)*	*2.40 (1.11, 5.17)*	2.50 (1.16, 5.41)
In last pregnancy	*Yes*	*1.65 (0.69, 3.92)*	*1.62 (0.68, 3.86)*	*1.62 (0.67, 3.91)*	*1.67 (0.69, 4.03)*	1.68 (0.70, 4.07)
NON-CLINICALLY INDICATED TERMINATIONS						
In any past pregnancy	*Yes*	*1.00 (0.69, 1.46)*	*0.99 (0.68, 1.44)*	*0.99 (0.68, 1.45)*	*1.02 (0.70, 1.48)*	1.04 (0.71, 1.51)
In last pregnancy	*Yes*	*0.97 (0.62, 1.53)*	*1.00 (0.63, 1.57)*	*1.02 (0.65, 1.62)*	*1.05 (0.66, 1.65)*	1.06 (0.67, 1.67)
MISCARRIAGE						
In any past pregnancy	Yes	1.25 (1.02, 1.53)	1.21 (0.98, 1.49)	1.29 (1.01, 1.64)	1.21 (0.98, 1.49)	1.32 (1.04, 1.68)
In last pregnancy	Yes	1.22 (0.99, 1.51)	1.21 (0.96, 1.52)	1.22 (0.97, 1.54)	1.22 (0.97, 1.53)	1.27 (1.00, 1.60)
1st TRIMESTER MISCARRIAGE						
In any past pregnancy	*Yes*	*1.28 (1.03, 1.59)*	*1.24 (0.99, 1.54)*	*1.32 (1.03, 1.68)*	*1.24 (0.99, 1.55)*	1.35 (1.06, 1.73)
In last pregnancy	*Yes*	*1.21 (0.95, 1.53)*	*1.19 (0.94, 1.53)*	*1.21 (0.94, 1.55)*	*1.21 (0.95, 1.54)*	1.25 (0.97, 1.61)
2nd TRIMESTER MISCARRIAGE						
In any past pregnancy	*Yes*	*0.98 (0.66, 1.44)*	*0.96 (0.65, 1.42)*	*0.98 (0.65, 1.47)*	*0.95 (0.64, 1.41)*	0.99 (0.66, 1.49)
In last pregnancy	*Yes*	*1.16 (0.75, 1.80)*	*1.14 (0.74, 1.78)*	*1.17 (0.75, 1.82)*	*1.17 (0.76, 1.81)*	1.20 (0.77, 1.87)
STILLBIRTH						
In any past pregnancy	Yes	1.71 (0.90, 3.23)	1.75 (0.94, 3.37)	1.82 (0.96, 3.48)	1.82 (0.96, 3.43)	1.91 (1.00, 3.65)
In last pregnancy	Yes	1.76 (0.90, 3.44)	1.74 (0.89, 3.42)	1.84 (0.93, 3.64)	1.89 (0.95, 3.73)	1.89 (0.96, 3.75)
LOW BIRTHWEIGHT						
In any past pregnancy	Yes	1.14 (0.79, 1.65)	1.13 (0.79, 1.64)	1.16 (0.80, 1.68)	1.15 (0.79, 1.65)	1.18 (0.81, 1.71)
In last pregnancy	Yes	1.44 (0.96, 2.17)	1.46 (0.97, 2.19)	1.45 (0.97, 2.17)	1.48 (0.99, 2.23)	1.48 (0.99, 2.22)
PRETERM DELIVERY						
In any past pregnancy	Yes	1.41 (1.00, 1.98)	1.39 (0.99, 1.95)	1.42 (1.01, 2.00)	1.36 (0.96, 1.91)	1.40 (0.99, 1.98)
In last pregnancy	Yes	1.70 (1.16, 2.47)	1.71 (1.18, 2.50)	1.72 (1.18, 2.50)	1.72 (1.18, 2.52)	1.73 (1.10, 2.52)

N.B. greyed out cells highlight odds ratios significant at $p<0.05$

Table A.2.7: Odds ratios for the association between past adverse outcomes and secondary infertility defined as TTP ≥ 12 months, including and excluding pregnancies conceived as a result of fertility treatment

		crude		Adjusted for age and year of pregnancy		Adjusted for age and year of pregnancy & no. of previous pregnancies	
		ALL OR (95% CI)	EXCLUDING INFERTILITY TREATMENT PREGNANCIES OR (95% CI)	ALL OR (95% CI)	EXCLUDING INFERTILITY TREATMENT PREGNANCIES OR (95% CI)	ALL OR (95% CI)	EXCLUDING INFERTILITY TREATMENT PREGNANCIES OR (95% CI)
TERMINATION							
In any past pregnancy	Yes	1.17 (0.83, 1.65)	**1.12 (0.77, 1.65)**	1.15 (0.82, 1.63)	**1.13 (0.78, 1.66)**	1.16 (0.82, 1.64)	**1.12 (0.77, 1.62)**
In last pregnancy	Yes	1.07 (0.72, 1.61)	**0.79 (0.46, 1.30)**	1.09 (0.73, 1.64)	**0.82 (0.49, 1.37)**	1.12 (0.74, 1.68)	**0.83 (0.50, 1.40)**
CLINICALLY INDICATED TERMINATIONS							
In any past pregnancy	*Yes*	*2.38 (1.12, 5.07)*	***1.84 (0.68, 4.99)***	*2.31 (1.07, 4.98)*	***1.80 (0.66, 4.92)***	*2.38 (1.10, 5.12)*	***1.83 (0.68, 4.95)***
In last pregnancy	*Yes*	*1.65 (0.69, 3.92)*	***0.33 (0.046, 2.41)***	*1.62 (0.68, 3.86)*	***0.32 (0.04, 2.34)***	*1.62 (0.67, 3.91)*	***0.32 (0.45, 2.28)***
NON-CLINICALLY INDICATED TERMINATIONS							
In any past pregnancy	*Yes*	*1.00 (0.69, 1.46)*	***1.04 (0.70, 1.54)***	*0.99 (0.68, 1.44)*	***1.05 0.71, 1.55)***	*0.99 (0.68, 1.45)*	***1.03 (0.69, 1.53)***
In last pregnancy	*Yes*	*0.97 (0.62, 1.53)*	***0.86 (0.50, 1.47)***	*1.00 (0.63, 1.57)*	***0.91 (0.54, 1.56)***	*1.02 (0.65, 1.62)*	***0.94 (0.55, 1.60)***
MISCARRIAGE							
In any past pregnancy	Yes	1.25 (1.02, 1.53)	**1.14 (0.91, 1.44)**	1.21 (0.98, 1.49)	**1.12 (0.89, 1.41)**	1.29 (1.01, 1.64)	**1.12 (0.86, 1.47)**
In last pregnancy	Yes	1.22 (0.99, 1.51)	**1.03 0.80, 1.32)**	1.21 (0.96, 1.52)	**1.01 (0.78. 1.31)**	1.22 (0.97, 1.54)	**1.01 (0.77, 1.32)**
1st TRIMESTER MISCARRIAGE							
In any past pregnancy	*Yes*	*1.28 (1.03, 1.59)*	***1.16 (0.91, 1.48)***	*1.24 (0.99, 1.54)*	***1.13 (0.88, 1.45)***	*1.32 (1.03, 1.69)*	***1.14 (0.87, 1.51)***
In last pregnancy	*Yes*	*1.21 (0.95, 1.53)*	***0.99 (0.75, 1.31)***	*1.19 (0.94, 1.53)*	***0.88 (0.74, 1.30)***	*1.21 (0.94, 1.55)*	***).98 (0.73, 1.30)***
2nd TRIMESTER MISCARRIAGE							
In any past pregnancy	*Yes*	*0.98 (0.66, 1.44)*	***0.99 (0.64, 1.51)***	*0.96 (0.65, 1.42)*	***0.97 (0.63, 1..49)***	*0.98 (0.65, 1.47)*	***0.96 (0.61, 1.51)***
In last pregnancy	*Yes*	*1.16 (0.75, 1.80)*	***1.14 (0.71, 1.86)***	*1.14 (0.74, 1.78)*	***1.14 (0.70, 1.85)***	*1.17 (0.75, 1.82)*	***1.13 (0.68, 1.85)***
STILLBIRTH							
In any past pregnancy	Yes	1.71 (0.90, 3.23)	**1.90 (0.97, 3.68)**	1.75 (0.94, 3.37)	**1.91 (0.99, 3.70)**	1.82 (0.96, 3.48)	**1.94 (0.99, 3.80)**
In last pregnancy	Yes	1.76 (0.90, 3.44)	**2.01 (0.99, 4.06t)**	1.74 (0.89, 3.42)	**2.02 (0.99, 4.13)**	1.84 (0.93, 3.64)	**2.01 (0.98, 4.13)**
ECTOPIC PREGNANCY							
In any past pregnancy	Yes	3.84 (2.30, 6.40)	**3.68 (2.07, 6.59)**	3.72 (2.25, 6.14)	**3.65 (2.07, 6.44)**	3.83 (2.30, 6.36)	**3.69 (2.06, 6.59)**
In last pregnancy	Yes	3.71 (2.04, 6.73)	**3.99 (2.08, 7.66)**	3.66 (2.02, 6.64)	**4.11 (2.16, 7,82)**	3.73 (2.06, 6.79)	**4.08 (2.13, 7.79)**
LOW BIRTHWEIGHT							
In any past pregnancy	Yes	1.14 (0.79, 1.65)	**1.30 (0.88. 1.92)**	1.13 (0.79, 1.64)	**1.28 (0.87, 1.88)**	1.16 (0.80, 1.68)	**1.29 (0.87, 1.92)**
In last pregnancy	Yes	1.44 (0.96, 2.17)	**1.59 (1.04, 2.45)**	1.46 (0.97, 2.19)	**1.59 (1.03, 2.43)**	1.45 (0.97, 2.17)	**1.60 (1.04, 2.44)**
PRETERM DELIVERY							
In any past pregnancy	Yes	1.41 (1.00, 1.98)	**1.52 (1.06, 2.20)**	1.39 (0.99, 1.95)	**1.51 (1.05, 2.18)**	1.42 (1.01, 2.00)	**1.53 (1.05, 2.22)**
In last pregnancy	Yes	1.70 (1.16, 2.47)	**1.75 (1.16, 2.63)**	1.71 (1.18, 2.50)	**1.76 (1.68, 2.66)**	1.72 (1.18, 2.50)	**1.78 (1.18, 2.69)**

N.B. greyed out cells highlight odds ratios significant at $p<0.05$

APPENDIX 3 Papers published (inside pocket)

- Manuscript on the prevalence of infertility (using NWHS Stage 1 data)

  Oakley L, Doyle P, Maconochie N. Lifetime prevalence of infertility and infertility treatment in the UK: results from a population-based survey of reproduction. *Hum. Reprod.* 2008;23(2):447-450.

- NWHS Methods paper (for reference purposes)

  Maconochie N, Doyle P, Prior S. The National Women's Health Study: assembly and description of a population-based reproductive cohort. *BMC Public Health* 2004;4:35.

- Manuscript on social inequalities in help-seeking and use of health services (using NWHS Stage 2 data)

  Morris M, **Oakley L**, Maconochie N, Doyle P. An investigation of social inequalities in help-seeking and use of health services for fertility problems in a population-based sample of UK women. *Hum Fertil.* 2010;Advance Access, December 1(doi:10.3109/14647273.2010.536609).

BMC Public H

Research article

Open Access

The National Women's Health Study: assembly and description of a population-based reproductive cohort

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Abstract

Background: Miscarriage is a common event but is remarkably difficult to measure in epidemiological studies. Few large-scale population-based studies have been conducted in the UK.

Methods: This was a population-based two-stage postal survey of reproductive histories of adult women living in the United Kingdom in 2001, sampled from the electronic electoral roll. In Stage 1 a short "screening" questionnaire was sent to over 60,000 randomly selected women in order to identify those aged 55 and under who had ever been pregnant or ever attempted to achieve a pregnancy, from whom a brief reproductive history was requested. Stage 2 involved a more lengthy questionnaire requesting detailed information on every pregnancy (and fertility problems), and questions relating to socio-demographic, behavioural and other factors for the most recent pregnancy in order to examine risk factors for miscarriage. Data on stillbirth, multiple birth and maternal age are compared to national data in order to assess response bias.

Results: The response rate was 49% for Stage 1 and 73% for the more targeted Stage 2. A total of 26,050 questionnaires were returned in Stage 1. Of the 17,748 women who were eligible on the grounds of age, 27% reported that they had never been pregnant and had never attempted to conceive a child. The remaining 13,035 women reported a total of 30,661 pregnancies. Comparison of key reproductive indicators (stillbirth and multiple birth rates and maternal age at first birth) with national statistics showed that the data look remarkably similar to the general population.

Conclusions: This study has enabled the assembly of a large population-based dataset of women's reproductive histories which appears unbiased compared to the general UK population and which will enable investigation of hard-to-measure outcomes such as miscarriage and infertility.

Background

Despite improvements in obstetric care in the UK over the past fifty years, it is estimated that around one in five pregnancies will end in miscarriage (fetal death before 24 weeks) [1,2]. The personal and public health impact of pregnancy loss is a neglected area in medical research and strategies of prevention remain outside mainstream medical services.

Although many large-scale population-based studies of miscarriage risk have been conducted elsewhere [3-10], relatively few such studies have been conducted in the UK,

and most of these have been occupational [11-14]. There are no registers of miscarriage or routine data collection systems which would allow linkage of miscarriages to individual women in the UK . There are thus no national prevalence estimates which can be used as reference for UK-based clinical or epidemiological studies. In addition, although there is now greater knowledge of how the risk of miscarriage changes with maternal age and previous history of miscarriage [6], the influence and interaction of biological, behavioural and social risk factors are less well-understood. The lack of reliable information on risk factors, and the confusion surrounding ad hoc reports of spurious associations, makes research in this area of great importance.

Studies of miscarriage have tended to be clinical-based, and are thus subject to selection bias. For example, gestations are later among miscarriages reaching hospital-based clinics. Many miscarriages are managed at home, and some are not reported to a clinician. Not only is miscarriage hard to measure, and different clinical sources rarely see the full range of cases, but reported risks of miscarriage tend to be pregnancy-rather than woman-based: estimates of risk tend to relate to the proportion of pregnancies ending in miscarriage, and there are very few studies examining the risk of experiencing one, two or more miscarriages, or the chances of conceiving following a miscarriage [15]. Large prospective cohort studies are theoretically the ideal design, but take time and are prohibitively expensive [2]. An alternative and practical approach is a survey asking the women themselves for their full reproductive history, including all fetal losses at all gestations.

An increasing number of couples are also seeking help for problems achieving a pregnancy. Although it is estimated that up to 15% couples experience such problems [16], few population-based prevalence studies have been conducted in the UK, particularly where fertility problems have been treated solely by the general practitioner using ovarian stimulation.

We now report on a large UK population-based survey of reproductive health, the National Women's Health Study. The study design was developed from several other large epidemiological surveys of reproductive outcome which showed that a postal method could be used to obtain full reproductive histories from large study populations [13,14,17,18]. The aim of the study was to obtain population-based prevalence estimates relating to miscarriage and infertility, and to obtain good quality data on potential risk factors for miscarriage to be used when advising and counselling women who have suffered miscarriage and those who wish to reduce their risk of future pregnancy loss. The design of the study, together with response rates and description of the study population, is presented in this report. Further reports on risk factors for miscarriage, plus population-based estimates of miscarriage and of pregnancies conceived using assisted reproduction techniques will follow.

Methods

Sample selection

This was a population-based cross-sectional postal survey of reproductive histories of adult women living in the United Kingdom in 2001, designed to enable the construction of a retrospective population-based reproductive cohort and a case-control study of risk factors for miscarriage. A sample of women was randomly selected from electronic electoral registers for England, Wales, Scotland and Northern Ireland held by the company *Eurodirect* [19]. All UK citizens aged 18 and over are eligible to vote; registration is voluntary, but in 2001 around 98% of the entire resident population were on the electoral register [20], the remainder being largely non-UK citizens and iterant population. At the time of survey there was no opt-out clause for those who did not wish to be on an electronic version of the electoral register, so the sampling frame contained all UK residents eligible (and registered) to vote.

In order to reduce possible biases associated with memory, we aimed for a sample aged 55 years and under at survey. Date of birth is not, however, routinely recorded on the electoral register. To avoid unnecessary mailing and expense, we therefore made use of a probabilistic process offered by *Eurodirect* based on forename, whereby the sampling frame was restricted to women thought likely to be aged 55 and under on the basis of their name. This process was based on empirical data relating to birth certificates going back to the beginning of the 20th century, from which it could be calculated that, for example, those named "Elsie" are likely to be aged over 55, and those named "Kylie" under 55 years. Predictions are further refined by examination of combinations of names within a household (a "Jane" married to or living with an Alfred likely to be older than a "Jane" married to or living with a "Darren") and length of residency (e.g. someone registered to vote at the same address for 12 years has to be over 30). We requested a random sample of 61,000 women likely to be aged 55 and under (sample size calculations based on achieving at least 80% power for key risk factors in the case-control analysis, and cost). After removing those known to be under age 18 at study (those turning 18 in the year of registration are allowed to register early, giving date of birth), the final sample consisted of 60,814 women.

The study received approval from the Trent Multi-Centre Research Ethics Committee and the Ethics Committee of the London School of Hygiene & Tropical Medicine.

Postal survey

The postal survey had two stages. Stage one consisted of a single-page "screening" questionnaire which asked for details of all pregnancies experienced by study participants, as well as periods of infertility and infertility treatment. This form was sent to the whole sample and included "opt-out" boxes to be ticked if the recipient had never been pregnant and had never attempted to have children, and/or was over age 55, and/or did not wish to take part. The second stage of the study consisted of a longer postal questionnaire which was sent to all those responding to Stage 1 who had ever been pregnant or who reported ever attempting to conceive and who agreed to be re-contacted. Excluded from this second stage were women who had had one or more termination for non-medical reasons (i.e. for reasons other than that a defect had been identified in the fetus or that continuing the pregnancy would put the mother at risk) and no other pregnancies. The Stage 2 questionnaire requested more general detail about the women (including height, age at menarche, educational level, marital status and details of infertility problems, treatment and diagnosis, if appropriate); detailed information on all pregnancies (including whether the pregnancy was the planned, the result of infertility treatment, father's date of birth and whether father had remained the same); plus socio-demographic and behavioural details relating to the most recent pregnancy. These details included questions relating to weight at start of pregnancy, nausea, smoking, coffee and alcohol consumption, diet, vitamin intake, ill health, air travel, sexual intercourse, occupation and stress levels. The most recent pregnancy was selected to minimise biases related to recall, and since it could be at the start, middle or end of the reproductive careers of these women whose ages at survey ranged from 18 to 55 years potential biases relating to ending reproductive careers on a "success" were not expected to be large. For those whose most recent pregnancy had ended in miscarriage (defined as fetal death at <24 weeks gestation), brief information relating to clinical management of miscarriage and the advice given was also requested. Permission to access clinical notes relating to outcomes reported in the questionnaire, and to contact the women for further study if needed, was also requested. In order to increase the number of cases for the case-control analysis of risk factors for miscarriage, women who had had a miscarriage recently (since 1995) but whose last pregnancy was not a miscarriage were sent a third questionnaire. This was a shortened version of the Stage 2 questionnaire, containing only those questions relating to biological, socio-demographic and behavioural details of the most recent pregnancy, but now requesting these details in relation to the most recent miscarriage. Such women then had two pregnancies in case-control analyses and standard errors were computed using a robust method based on the "sandwich estimate" to account for this statistically.

A free telephone helpline was run throughout the study, to answer queries and refer on to other organizations for professional help, if appropriate, and this was well used.

Statistical methods

All analyses in this paper were performed using Stata statistical software [21]. To investigate possible selection bias we compared stillbirth and multiple delivery rates with rates in the general population. For this we obtained annual registered stillbirth risks and registered multiple delivery rates by maternal age for England and Wales, 1980–2001 [22] (data for 2002 was estimated from that for 2001). Standardised registered stillbirth ratios (SRSR) and standardised multiple delivery rates (SMDR) were then calculated using logistic regression analysis (offsetting the log odds of the population risk) [23]. The unit of analysis for stillbirths was a registered birth. A registered livebirth is defined as a baby born alive at any gestation, registered stillbirth being defined as a fetal death at 28 weeks or more gestation until the end of 1992, and at 24 weeks or more gestation from 1993 onwards. Where gestational age was not available from Stage 2 data, a pregnancy was considered to be a stillbirth if it was so described. Forty-one (40%) of the total 102 stillbirths in the analysis fell into this category. For multiple delivery, the unit of analysis was a pregnancy containing at least one livebirth or registered stillbirth (as described above). For the purposes of the analyses presented in this paper (comparisons with the general population), a pregnancy was only considered multiple if it contained two or more babies who were liveborn or (registered) stillborn in order to be consistent with the definitions used in the national data. Thus, for example, a twin pregnancy occurring before 1993 and resulting in a livebirth and a fetal death at less than 28 weeks was considered to be a singleton pregnancy in this analysis. Average maternal age at first birth, if live, was also compared with that in the general population. Annual average maternal age at first (registered) birth, if live, was obtained with denominators for England and Wales, 1980–2001 [22] and re-calculated for 5-year periods. This national data was available for births within marriage only. Marital status of mother at time of birth was known only for the most recent pregnancy (or most recent miscarriage since 1995) in this dataset. For the NWHS average maternal age was therefore calculated for all first registered births, if live. No formal statistical comparisons of maternal age were made, partly because the numbers were so large that slight, non-meaningful, nuances in the data would give a statististically significant

Table 1: The National Women's Health Survey – response rates

STAGE 1	No.	Crude %	Adjusted[1] %
TOTAL QUESTIONNAIRES POSTED	*60,814*	*100%*	-
Returned undelivered[2]	3,661	6%	-
Responded	26,050	43%	46%
Did not wish to participate	2,738	5%	5%
Aged >55 years or otherwise ineligible[3]	5,564	9%	10%
Aged < = 55 years but never attempted to have children	4,713	8%	8%
Aged < = 55, ever attempted to have children	13,035	21%	23%
Among whom,			
- Never pregnant	*340*	*3%*	-
- Ever pregnant	*12,695*	*97%*	-
STAGE 2			
TOTAL QUESTIONNAIRES POSTED	*10,828*	*100%*	-
Returned undelivered	16	0.2%	-
Responded	7,882	73%	73%
No longer wished to participate	180	2%	2%
Completed questionnaire	7,702	71%	71%
Among whom,			
- Attempted pregnancy, never pregnant	*194*	*3%*	
- Ever pregnant[4]	*7,508*	*97%*	

[1] Adjusted for undelivered mail [2] Includes 70 women who died before the study start [3] Under 18 at study start (6th November 2001); male; foreign national; or too ill to participate [4] 344 women who had had a miscarriage since 1995, but whose last pregnancy was not a miscarriage, were sent a second stage 2 questionnaire and were asked to supply details in relation to their most recent miscarriage. 285 (83%) of the women responded to this third questionnaire.

result, and render the comparison meaningless, and partly because the average ages in the general population, though comparable, were expected to be similar but slightly older in the general population data owing to the fact that the data related to births within marriage only. Births where the date of birth or maternal age were not known were excluded from all comparisons with population data.

Results

Stage 1

The response to the first stage of the study is summarised in Table 1. 29,721 (49%) of all the questionnaires were returned to us, though for 3,591 (6%) this was to say that the addressee had moved, and for 70 (0.1%) that the woman had died. A total of 26,050 questionnaires were returned by the addressee, a response rate of 46% assuming that all questionnaires not returned undelivered had reached the correct recipient. Of these, 11% (5% overall) did not wish to participate in the study, and a further 21% were aged over 55 (n = 5,499) or were otherwise ineligible (n = 65). 27% of the 17,748 women who were eligible on the grounds of age, reported that they had never been pregnant and had never attempted to conceive a child, the remaining 13,035 women reporting their full reproductive history.

12,695 women aged under 55 at survey had been pregnant at least once. These 12,695 women, whose average age at survey was 40.5 years, had started their reproductive careers from 1963 to 2002, 75% having their first pregnancy in 1980 or later (Table 2). 486 women had conceived their first pregnancy less than 40 weeks before the study commenced, 126 of whom were pregnant when they filled in the questionnaire. Overall these 12,695 women reported a total of 30,661 pregnancies, 80% of which occurred in 1980 or later. Outcome of these pregnancies is described in Table 2.

Stage 2

11,424 (88%) women ever attempting to have children (successfully or unsuccessfully) agreed to participate in the second stage of the study. Of these 596 (5%) were not sent a Stage 2 questionnaire, 212 because they had only ever had one or more termination of pregnancy for non-medical reasons, and 384 because their Stage 1 form arrived back after mailing had ended. A total of 10,828 women were thus sent a second stage questionnaire. The response to this second stage was high (73%), though 2% of women had decided that they no longer wished to participate (Table 1). The 7,702 women completing a Stage 2 questionnaire, and the 18,391 pregnancies they reported, are described in Table 2. Their characteristics are almost

Table 2: NWHS Stages 1 and 2 – description of women reporting one or more pregnancy, and of the pregnancies they reported

	STAGE 1 n	(%)	STAGE 2 n	(%)
TOTAL NO. WOMEN IN ANALYSIS	**12,695**	**(100)**	**7508**	**(100)**
Age at survey (years)				
<30	1247	(9.8)	685	(10.6)
30–34	2007	(15.8)	1284	(20.6)
35–39	2618	(20.6)	1629	(28.6)
> = 40	6678	(52.6)	3910	(39.3)
Not known	145	(1.1)	-	
Mean age (SD)[1]	*40.5 (8.45)*		*40.4 (8.24)*	
Year of first pregnancy				
<1980	3201	(25.2)	1798	(24.0)
1980–84	1902	(15.0)	1131	(15.1)
1985–89	2091	(16.5)	1259	(16.8)
1990–94	2158	(17.0)	1356	(18.1)
1995–99	2079	(16.4)	1406	(18.7)
2000–02	788[2]	(6.2)	558[3]	(7.4)
Not known	476	(3.8)	-	
Total number of pregnancies reported per woman				
1	2607	(20.5)	1403	(18.7)
2	5077	(40.0)	3162	(42.1)
3	2962	(23.3)	1749	(23.3)
4	1573	(12.4)	818	(10.9)
5	285	(2.2)	229	(3.1)
> = 6	191	(1.5)	147	(1.9)
Median (range)	*2 (1 – 18)*		*2 (1 – 18)*	
Pregnancy history				
No dates given for any pregnancies	436	(3.4)	-	
All pregnancies occurred before 1980	1495	(11.8)	853	(11.4)
Pregnancies before and after 1980	1707	(13.5)	945	(12.6)
Pregnancy history commenced 1980 onwards	9057	(71.3)	5710	(76.1)
All pregnancies conceived after 31/03/2000	*486*	*(3.8)*	*329*	(4.4)
TOTAL REPORTED PREGNANCIES	**30661**	**(100)**	**18391**	**(100)**
Outcome of pregnancy				
Livebirth, surviving >7 days	24081	(78.9)	14782	(80.4)
Livebirth, early neonatal death	95	(0.3)	56	(0.3)
Stillbirth	188	(0.6)	110	(0.6)
Miscarriage[4]	3512	(11.5)	2326	(12.7)
Ectopic	226	(0.7)	102	(0.6)
Termination for medical reasons[5]	312	(1.0)	89	(0.5)
Termination for non-medical reasons[6]	1424	(4.6)	562	(3.1)
Molar pregnancy	47	(0.2)	26	(0.1)
Ongoing (current) pregnancy	482	(1.6)	338	(1.8)
Not known	294	(1.0)	-	
Year of pregnancy end				
<1980	6093	(19.9)	3486	(18.0)
1980–84	4503	(14.7)	2623	(14.3)
1985–89	5028	(16.4)	3000	(16.3)
1990–94	5549	(18.1)	3434	(18.7)
1995–99	5808	(18.9)	3865	(21.0)
2000–02	2721[7]	(8.9)	1983[8]	(10.8)
Not known	959	(3.1)	-	

[1] Where date of birth given [2] Includes 486 women whose first pregnancy was conceived after 31st March 2000, 126 of whom were currently pregnant for the first time at time of survey [3] Includes 329 women whose first pregnancy was conceived after 31st March 2000, 73 of whom were currently pregnant for the first time at time of survey [4] Fetal death at <24 weeks gestation. Includes missed miscarriages (fetal death at <24 weeks without spontaneous expulsion of fetus) and blighted ova (anembryonic pregnancy) [5] Termination of pregnancy because of a defect identified in the baby, or because continuing the pregnancy would put the mother's health at risk [6] Termination of pregnancy for reasons other than a defect identified in the baby or risk to mother's health [7] 1,718 of these pregnancies were conceived after 31st March 2000 [8] 1,232 of these pregnancies were conceived after 31st March 2000

Table 3: Comparison with population birth data of reported births in Stages 1 and 2[1] of the National Women's Health Study occurring since 1980[2]

REGISTERED STILLBIRTH[3]					
		No. stillbirths[3]	Total livebirths & stillbirths[3]	SRSR[4] (95% CI)	
Stage 1	1980–2002	102	18,740	115	(94 – 139)
Stage 2	1980–2002	59	12,061	102	(79 – 132)
MULTIPLE (REGISTERED) DELIVERY[5]					
		No. multiple deliveries[5]	Total deliveries[5]	SMDR[4] (95% CI)	
Stage 1	1980–2002	264	18,391	111	(99 – 126)
Stage 2	1980–2002	169	11,887	108	(93 – 126)
AVERAGE MATERNAL AGE AT FIRST[6](LIVE)BIRTH (years)					
		No. first[6] livebirths	Mean (SD) age[7]	England & Wales[8] Mean age	
Stage 1	Year of delivery				
	1980–84	1,724	25.2 (4.12)	25.5	
	1985–89	1,916	25.9 (4.56)	26.4	
	1990–94	2,058	27.1 (4.85)	27.8	
	1995–99	2,026	28.6 (5.01)	29.0	
	2000–02	699	29.4 (5.06)	29.6	
Stage 2	1980–84	1,032	25.5 (4.02)	25.5	
	1985–89	1,182	26.0 (4.45)	26.4	
	1990–94	1,325	27.3 (4.78)	27.8	
	1995–99	1,432	28.8 (4.81)	29.0	
	2000–02	540	29.7 (4.89)	29.6	

[1] Stage 2 data are a subset of Stage 1 data (see methods). [2] Pregnancies with missing maternal age have been excluded from this analysis. [3] Registered stillbirths 1980–2002, defined as fetal death at ≥ 28 weeks prior to 1992, or at ≥24 weeks thereafter. 41 (40%) of stillbirths had no gestational age, but were described as stillbirths by the mother. Unit of analysis is a baby; multiple births counted as many times as there are babies. Denominator contains all reported livebirths and registered stillbirths 1980–2002. [4] Standardised Registered Stillbirth Ratio (SRSR) and Standardised registered Multiple Delivery Ratio (SMDR). Standardised for maternal age (5-year intervals) and single year of birth using data for England and Wales 1980–2002. [5] Unit of analysis is a delivery (pregnancy) containing one or more registered live or stillbirth; multiple pregnancies counted once only. Multiple pregnancies containing only one registered birth (with another non-registrable outcome, such as miscarriage) considered as singleton in this analysis. [6] First registered birth, if live. [7] NWHS data relates to livebirths both within and outside marriage [8] Livebirths within marriage only

identical to those of Stage 1, indicating that Stage 2 responders were an apparently unbiased subset of those responding to Stage 1. 5,777 (75%) women responding to Stage 2 gave signed consent for us to access their medical notes, with 6,963 (90%) agreeing to be contacted again in the future, if required.

Comparison with national data

Comparisons of Stage 1 data, and the subset Stage 2 data, with national rates are presented in Table 3. There was no evidence to suggest that stillbirth differed from expectation in either Stage 1 (SRSR 115 (95% CI 94 - 139), P = 0.17), or Stage 2 data (SRSR 102 (95% 79 - 132), P = 0.86). Multiple delivery was also in line with expectation from national rates for both stages (Stage 1 SMDR 111 (95% CI 99 - 126), P = 0.08), Stage 2 SMDR 108(95% CI 93–126, P = 32)). Although the inference from this is unambiguous for both stages of the study, the point estimates were noted to be closer to unity for Stage 2 data where almost all pregnancies had known gestational age. This reflects the fact that there might be some slight misclassification of registered stillbirth prior to 1993 in the

Stage 1 data where gestational age was only known for 61% of reported stillbirths, some of which might legally be classified as miscarriages.

Age at first (live) birth was remarkably similar to national data for both Stage 1 and Stage 2 data (Table 3). Exactly as expected, though showing no evidence to suggest any biases with respect to maternal age, average age at first birth was very slightly higher for the national data, since it related to births within marriage only, whereas the NWHS data related to all births (marital status at delivery was unknown).

Discussion

Using a novel method, the National Women's Health Study has enabled a large UK population-based dataset to be assembled, comprising full reproductive histories, including any history of infertility, for 13,035 women, 12,695 of whom had conceived 30,661 pregnancies. We have obtained further detailed information for 7,702 of these women (18,391 pregnancies), including fertility diagnoses for both male and female partner (if appropriate), and lifestyle and behavioural risk factors for the most recent pregnancy. Seventy-five percent of these women consented to their medical notes being accessed in relation to information reported in the questionnaire, and 90% agreed to be contacted again, thus providing the means to carry out a population-based cohort study of these women at some time in the future.

UK population-based data, collected at government level by England & Wales, Scotland and Northern Ireland, relate to registered births (live and still) and terminations of pregnancy, with Scotland also routinely collecting maternity data on hospital deliveries at any gestation. The National Women's Health Study goes one step further than this, providing the whole reproductive picture. Rather than being a pregnancy-based, cross-sectional survey, the data collected for each woman covers the complete spectrum of reproductive outcomes from infertility problems through miscarriage, ectopic pregnancies and terminations (for both medical and non-medical reasons), to live and stillbirths, and does not rely on legal definitions for inclusion in the dataset. Furthermore, unlike most epidemiological studies of adverse reproductive outcome such as miscarriage, the data source is not clinical (which, for miscarriage, leads to inevitable biases relating to gestational age), but relates to women selected randomly from the UK electoral register. And for outcomes such as infertility no other data currently exist to enable estimation of how many pregnancies in the population as a whole result from fertility treatment.

The study does rely on maternal recall and this could be a source of bias. Studies of self-reported reproductive history and exposures relating to reproductive events have, however, found maternal recall to have acceptably high reliability, and to be little affected by time from event [24-26].

In terms of the key reproductive indicators of stillbirth, multiple delivery rates and maternal age at first birth, the data look remarkably similar to the general population. We therefore feel confident that response was unlikely to be related to adverse reproductive outcome. Indeed, the average age at survey of around 40 years, coupled with average ages at first birth which are exactly as would be expected from general population data, could be seen to indicate that non-responders to the survey tended to concentrate among younger women who had not yet tested their fertility. In addition, we feel confident that those responding to the more detailed Stage 2 questionnaire are an unbiased sample of those responding to Stage 1. Both Stage 1 and Stage 2 data can thus can be considered unbiased with respect to reproduction, and representative of patterns among all women in the UK population who have ever tried to have children, hence prevalence estimates might be taken as unbiased estimates of hard-to-measure outcomes such as miscarriage and pregnancies conceived through assisted reproduction techniques. Such data will be invaluable as population-based reference data for epidemiological studies of reproduction.

In addition to both pregnancy-and woman-based population prevalence estimates, further papers to follow include reports of case-control analyses of behavioural and lifestyle risk factors for miscarriage.

Conclusions

In summary, we have assembled a large population-based dataset of women's reproductive histories which appears representative of the general UK population and which will enable investigation of hard-to-measure outcomes such as miscarriage and infertility.

Competing interests

None declared

Authors' contributions

NM and PD initiated the research and participated in protocol design, data collection, analysis and writing the paper. SP participated in data collection and analysis. All authors read and approved the final manuscript.

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APPENDIX 3
Manuscript on social inequalities in help-seeking and use of health services
Morris 2010
(Paper 3)

An investigation of social inequalities in help-seeking and use of health services for fertility problems in a population-based sample of UK women

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Abstract
Although infertility is an important public health problem, treatment can be expensive and resources are increasingly scarce. This study investigates possible inequalities in the use of medical services for fertility problems. We analysed data from a population-based survey for associations between socio-economic characteristics and help-seeking or use of services, to establish whether inequalities existed. More women of higher social status and education reported fertility problems, but there was no clear trend in help-seeking, investigations or treatments for infertility by social status and education level. New work is planned to investigate these issues more fully, particularly the role of family income.

Keywords: *Social inequalities, fertility treatment, health services, infertility, fertility problems, help-seeking*

Introduction

Infertility is an important public health problem thought to affect up to 15% of women of reproductive age at any one time (Boivin et al., 2007), and apart from pregnancy itself it is the most common reason for women aged 20–45 to consult their GP (Human Fertilisation and Embryology Authority, 2007).

Although a number of demographic and lifestyle factors have been identified as being consistently associated with infertility, evidence relating to the association between socio-economic indicators and infertility-related outcomes is equivocal.

The NICE 2004 guidelines for medical practitioners (National Collaborating Centre for Women's and Children's Health, 2004) provide a very clear suggested course of management, starting from initial investigations which can be carried out in primary care to the treatment a couple may receive in a specialist centre. We previously reported that 16% of women aged 40–55 in this UK population-based sample had sought advice from a doctor due to difficulties in conceiving (Oakley et al., 2008). However, it has been estimated that 56% of couples experiencing problems in conceiving seek advice and treatment (Boivin et al., 2007). Several UK studies have reported that higher socio-economic groups and/or more highly educated women are disproportionately represented among those seeking and receiving infertility treatment (Bunting & Boivin, 2007). This association has been confirmed in international studies carried out in settings with similar access to infertility treatment (Terävä et al., 2008).

The over-representation of women from higher socio-economic classes among births resulting from assisted reproductive technology (ART) is likely to be partly attributable to costs, both in terms of initiation of care and ability to continue treatment until a birth is achieved. Current National Institute for Health and Clinical Excellence (NICE) guidance recommends that up to three cycles of IVF are provided on the NHS for eligible couples. However, the Human Fertilisation and Embryology Authority (HFEA) stated in its 2003–2004 report that 25% of

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IVF cycles are NHS-funded (Human Fertilisation and Embryology Authority, 2007) and a survey of licensed IVF centres conducted in 2005 found that in the majority of cases only one NHS-funded cycle was provided (Kennedy et al., 2006).

This article reports data from the National Women's Health Study, a UK population-based cross-sectional study of women's reproductive histories. The aim of our analysis was to investigate the association between the socio-economic indicators of occupation and education, and not only self-reporting of infertility (here defined as trying to conceive for over 12 months) and treatment-seeking for infertility, but also access to investigations, any treatment and successful fertility treatment.

Methods

The NWHS, undertaken in 2001–2002, was originally designed to enable the construction of a retrospective UK population-based reproductive cohort and a case–control study of risk factors for miscarriage. The study population consisted of women believed to be 55 years old or younger chosen randomly from the UK electoral register. Full details of the methods have been published elsewhere (Maconochie et al., 2004).

The survey itself was conducted in two stages: Stage 1 comprised a screening questionnaire, asking for the woman's reproductive history, including periods of infertility and infertility treatment (Maconochie et al., 2004). Twenty-six thousand and fifty (46%) of these were returned by the addressee. To verify that the results would be generalisable and that the women responding were representative of the general population in terms of their reproductive histories, the data were examined against national statistics for relevant reproductive markers (maternal age at first birth, stillbirth and multiple delivery rates by maternal age). These analyses provided no evidence of statistical differences or biases between the survey data and expectation from national data with respect to patterns of reproduction (Maconochie et al., 2004).

Stage 2 consisted of a more detailed questionnaire sent to 10828 Stage 1 responders who had reported ever being pregnant or trying to conceive. 7702 women (71.1%) responded to the second stage questionnaire, of whom 194 (2.5%) had never achieved a pregnancy and two were currently pregnant for the first time. The Stage 2 questionnaire collected information about socio-demographic indicators alongside questions on fertility problems (e.g. help-seeking) and the details of pregnancies experienced (e.g. the outcome and whether it had resulted from assisted conception). Detailed questions were asked about behaviour, lifestyle and factors related to socio-economic status (SES) (e.g. occupation). The latter were asked in relation to the woman's last (most recent) pregnancy in order to try and minimise the potential for recall bias. This information was therefore not collected for the women who had never achieved a pregnancy.

Analysis strategy

Separate analyses were performed for the following five outcomes: (1) reporting problems getting pregnant; (2) ever consulting a doctor about these problems; (3) ever having (±partner ever having) fertility investigations; (4) ever having fertility treatment and (5) ever conceiving a pregnancy through fertility treatment. Each analysis was restricted to those women 'at risk' of the outcome. For instance, only those who reported consulting a doctor were included in the analysis of whether the women had had fertility investigations.

SES was coded using information on the reported occupation of the woman's husband/partner during the last pregnancy and was therefore only available for women who had ever been pregnant. The husband/partner's occupation was felt to be the best reflection of relative economic and social position as 42% of the women reported that they themselves were 'at home' ($n=2835$, 38%), unemployed or a student. All women in Stage 2 were asked what their highest attained qualification was at the time of the survey. Since the factors of interest (SES and educational level) are both proxy measures of health-related behaviour and are thus potentially highly correlated, they were not included in the same models. Several variables were potentially associated with both fertility-related outcomes and a woman's educational level or SES (i.e. were potential confounding factors). These were: the year in which a woman sought help, her age at survey, gravidity and age when she first tried to get pregnant.

All data were analysed using STATA 11.0 software. Associations between the principle factors of interest (SES/education) and the various outcomes were examined using multiple logistic regression analysis. Statistical significance was assessed through comparison of the fit of models with and without the factor of interest using likelihood ratio tests (LRT). Confounding was assessed through examination of changes in the estimates following inclusion of potential confounding factors. Age and gravidity were included in all analyses, however, for completeness and to enable comparison with the literature. In all analyses, $p=0.05$ was taken as the level for statistical significance.

The NWHS received ethical approval from both Trent Multi-centre Research Ethics Committee (MREC) and the research institution (London School

of Hygiene & Tropical Medicine). The authors of the NWHS data approved its use in this analysis.

Results

Study population

Among the 7702 women responding to the Stage 2 survey, the average age was 40.3 years (SD 8.3), 52% ($n = 4001$) being over the age of 40. The majority (78%; $n = 6035$) reported two or more pregnancies. Five percent of the women ($n = 393$) had never had a live birth and 2.5% ($n = 194$) had never achieved a pregnancy. The majority of women reporting at least one live birth had their first child in their twenties (67.2%; $n = 5178$).

Over 50% of the study population had been educated to A level or higher ($n = 4122$, 53.5%), while 9.3% had no qualifications at all ($n = 719$). Information was missing on this variable for 139 (1.8%) women. Among women with at least one pregnancy, 44% ($n = 3402$) were in the highest SES category (I and II). SES was not available for the 196 women (2.5%) who had never been pregnant or were currently pregnant for the first time ($n = 2$).

Reporting of fertility problems

Almost a fifth (19.3%, $n = 1486$) of the women in this sample reported problems getting pregnant in this survey. There was a clear trend of decreasing likelihood of reporting problems conceiving with decreasing levels of educational achievement, regardless of age and gravidity at time of trying (p for trend = 0.003). Women in the two lowest educational categories were around 20% less likely than those with a college degree to report that they had problems conceiving, whereas those with A levels or equivalent showed little evidence of a difference from those with a degree (Table I). Among women who had ever conceived (for whom SES information was available), there was also a clear trend of decreasing reporting of fertility problems with decreasing social class (p for trend = 0.001, Table I), the lowest group being almost 30% less likely to report problems than the highest.

Seeking medical help, having investigations, and having treatment for infertility

In this sample, 16.3% ($n = 1256$) women had consulted a doctor at some time about problems conceiving, representing 84.5% of those reporting problems overall (although 52 women who stated they sought help for fertility problems, also reported no problems conceiving). Of these 1256 women, 81.1% ($n = 1019$; 13.2% overall) went on to have investigations into a possible cause of the couple's problems, and 616 (49.0%) of those consulting a doctor (8.0% overall) underwent fertility treatment of some kind.

The prevalence of these outcomes by educational status and SES is shown in Table I. There is some suggestion that women with lower or no qualifications might be less likely to consult a doctor about problems conceiving, or to have investigations or ART treatment, but there was no statistical evidence of a trend (all $p \geq 0.05$). Among women who had ever conceived, there was no evidence of differences in the probability of seeking help, being investigated or being treated for infertility by SES.

Conceiving a pregnancy following treatment

There were 327 women who reported conceiving a pregnancy after having fertility treatment (53.1% of those who had treatment, 4.4% of women reporting any pregnancies). Women without academic qualifications appeared less likely to conceive than women who had a degree (Table I). Among women with formal qualifications there was no evidence of an effect of educational attainment on probability of conception (Table I).

Among women who had ever been pregnant (and had ever undergone fertility treatment), there was no evidence of an effect of SES on likelihood of conception following treatment (Table I).

Discussion

In this UK population-based sample of women, higher educational level and SES were associated with increased likelihood of reporting fertility problems. However, the association between these socioeconomic indicators and seeking help for fertility problems, undergoing fertility investigations, receiving fertility treatment or conceiving a pregnancy through treatment was not clearly demonstrated.

The higher rate of reporting fertility problems seen in higher SES women and those with more education is unlikely to be explained by delaying conception because we adjusted for the possible confounding effects of age. Further, existing literature lends little support to the hypothesis that there is a true difference in fertility by SES. The most plausible explanation for our findings is that it is the recognition and/or reporting of fertility problems – which is the first step toward seeking help (White et al., 2006) – and not fertility problems *per se*, which differs by SES. Higher education levels have been found to be associated with greater use of fertility services in the US (Bitler & Schmidt, 2006; Eisenberg et al., 2010) and in Scandinavia.(Wulff et al., 1997; Terävä et al., 2008). It is possible that

Table I. The association between different fertility-related outcomes and women's education level and socio-economic status.

Total women in survey: $N = 7702$	*n* (%)	Crude OR (95% CIs)	Adjusted OR* (95% CIs)
Reported ever having fertility problems: $n = 1486$			
Highest qualification			
Degree/equivalent	551 (22.2)	1	1
A level/equivalent	323 (19.7)	0.86 (0.74–1.01)	0.91 (0.77–1.07)
CSE, GCSE/equivalent	479 (17.6)	0.76 (0.66–0.87)	0.80 (0.69–0.93)
No qualifications	111 (15.4)	0.67 (0.54–0.83)	0.78 (0.61–1.00)
Total	*1464 (19.4)*		$p_{trend\ (1df)} = 0.003$
Missing [% women reporting problems]	*22 [1.5]*		
SES (among gravid women†)			
I/II (professional & managerial)	585 (18.4)	1	1
III (skilled non-manual)	119 (17.7)	0.98 (0.79–1.21)	0.99 (0.80–1.23)
III (skilled manual)	339 (16.1)	0.86 (0.74–0.99)	0.90 (0.77–1.05)
IV/V (partly unskilled & unskilled)	160 (14.6)	0.79 (0.65–0.94)	0.82 (0.68–1.00)
Unemployed/student	40 (13.7)	0.72 (0.51–1.00)	0.71 (0.50–1.01)
Total	*1243 (16.9)*		$p_{trend\ (1df)} = 0.001$c
Missing [% women reporting problems]	*47 [3.2]*		
Not collected† [% women reporting problems]	*196 [13.2]*		
	n (%)	Crude OR (95% CIs)	Adjusted OR* (95% CIs)
Sought medical help for fertility problems (among 1486 women with reported problems): $n = 1204$			
Highest qualification			
Degree/equivalent	440 (79.9)	1	1
A level/equivalent	267 (82.7)	1.21 (0.84–1.72)	1.17 (0.81–1.70)
CSE, GCSE/equivalent	390 (81.4)	1.11 (0.81–1.51)	1.10 (0.79–1.53)
No qualifications	87 (78.4)	0.91 (0.56–1.50)	0.89 (0.52–1.52)
Total	*1184 (80.9)*		$p_{trend\ (1df)} = 0.930$
Missing [% women seeking help]	*20 [1.7]*		
SES (gravid women only†)			
I/II (professional & managerial)	461 (78.8)	1	1
III (skilled non-manual)	96 (80.7)	1.12 (0.68–1.84)	1.12 (0.68–1.84)
III (skilled manual)	261 (77.0)	0.90 (0.65–1.24)	0.85 (0.61–1.19)
IV/V (partly unskilled & unskilled)	125 (78.1)	0.96 (0.63–1.47)	0.92 (0.59–1.43)
Unemployed/student	32 (80.0)	1.08 (0.48–2.39)	1.15 (0.51–2.63)
Total	*975 (78.4)*		$p_{trend\ (1df)} = 0.627$‡
Missing [% women seeking help]	*39 [3.2]*		
Not collected† [% women seeking help]	*190 [16.8]*		
	n (%)	Crude OR (95% CIs)	Adjusted OR* (95% CIs)
Ever had fertility investigations (among 1204 women who sought help): $n = 1019$			
Highest qualification			
Degree/equivalent	374 (82.2)	1	1
A level/equivalent	229 (82.4)	1.01 (0.68–1.50)	1.11 (0.74–1.66)
CSE, GCSE/equivalent	323 (79.8)	0.85 (0.61–1.20)	0.90 (0.63–1.30)
No qualifications	76 (79.2)	0.82 (0.48–1.42)	0.88 (0.49–1.57)
Total	*1002 (81.2)*		$p_{trend\ (1df)} = 0.494$
Missing [% women who had investigations]	*17 [1.7]*		
SES (gravid women only†)			
I/II (professional & managerial)	397 (81.7)	1	1
III (skilled non-manual)	77 (79.4)	0.86 (0.50–1.49)	0.84 (0.49–1.46)
III (skilled manual)	211 (76.7)	0.74 (0.51–1.06)	0.73 (0.50–1.07)
IV/V (partly unskilled & unskilled)	108 (81.2)	0.97 (0.59–1.58)	0.94 (0.56–1.56)
Unemployed/student	24 (66.7)	0.45 (0.22–0.93)	0.41 (0.19–0.88)
Total	*817 (79.6)*		$p_{trend\ (1df)} = 0.075$‡
Missing [% women who had investigations]	*28 [2.8]*		
Not collected† [% women who had investigations]	*174 [17.1]*		

(continued)

Table I. (*Continued*).

Total women in survey: $N=7702$	*n* (%)	Crude OR (95% CIs)	Adjusted OR* (95% CIs)
	n (%)	Crude OR (95% CIs)	Adjusted OR[§] (95% CIs)
Ever had fertility treatment (among 1204 women who sought help): $n=615$			
Highest qualification			
Degree/equivalent	222 (48.8)	1	1
A level/equivalent	145 (52.0)	1.14 (0.84–1.53)	1.29 (0.93–1.79)
CSE, GCSE/equivalent	199 (49.0)	1.01 (0.77–1.32)	1.00 (0.74–1.35)
No qualifications	39 (40.6)	0.72 (0.46–1.12)	0.84 (0.51–1.38)
Total	*605 (49.0)*		$p_{trend\ (1df)}=0.619$
Missing [% women who had treatment]	*10 [1.6]*		
SES (gravid women only[†])			
I/II (professional & managerial)	240 (49.4)	1	1
III (skilled non-manual)	50 (51.6)	1.09 (0.71–1.69)	1.06 (0.67–1.68)
III (skilled manual)	116 (42.2)	0.75 (0.56–1.01)	0.79 (0.57–1.10)
IV/V (partly unskilled & unskilled)	67 (50.4)	1.04 (0.71–1.52)	1.13 (0.73–1.73)
Unemployed/student	8 (22.2)	0.29 (0.13–0.66)	0.33 (0.14–0.77)
Total	*481 (46.8)*		$p_{trend\ (1df)}=0.152$c
Missing [% women who had treatment]	*24 [3.9]*		
Not collected[†] [% women who had treatment]	*110 [17.9]*		
	n (%)	Crude OR (95% CIs)	Adjusted OR* (95% CIs)
Ever conceived a pregnancy through fertility treatment (among 615 women who had fertility treatment): $n=324$			
Highest qualification			
Degree	119 (65.0)	1	1
A level/equivalent	78 (63.9)	0.95 (0.59–1.54)	0.85 (0.51–1.40)
GCSE/equivalent	107 (66.5)	1.07 (0.68–1.67)	0.97 (0.60–1.57)
No qualifications	15 (44.1)	0.42 (0.20–0.89)	0.34 (0.16–0.76)
Total	*319 (63.8)*		$p_{trend\ (1df)}=0.124$
Missing [%women who conceived through treatment]	*5 [1.5]*		
SES (gravid women only[†])			
I/II (professional & managerial)	162 (66.9)	1	1
III (skilled non-manual)	27 (54.0)	0.58 (0.31–1.07)	0.61 (0.32–1.15)
III (skilled manual)	76 (65.5)	0.94 (0.59–1.50)	0.92 (0.56–1.50)
IV/V (partly unskilled & unskilled)	41 (60.3)	0.75 (0.43–1.31)	0.79 (0.44–1.41)
Unemployed/student	3 (37.5)	0.30 (0.07–1.27)	0.31 (0.07–1.41)
Total	*309 (37.5)*		$p_{trend\ (1df)}=0.244$[‡]
Missing [% women who conceived through treatment]	*15 [4.6]*		

*Adjusted for woman's age at first trying and gravidity.
[†]SES was not available for the 196 women with gravidity = 0 because questions about occupation (used to code SES) were only asked in relation to the last pregnancy.
[‡]Test for trend excludes the 'Unemployed/student' category, which differs in a non-quantifiable way from the other SES groups.
[§]Adjusted for woman's age at first trying and gravidity and year in which she consulted first a doctor.

women with higher levels of education are more aware of how long conception might typically take, and possibly have greater expectations of what medical help they can access, and so be quicker to report their delay in conceiving as a fertility problem. This hypothesis is consistent with the results of a recent UK survey which found that women who met the criteria for infertility but had not sought help were characterised by, amongst other things, a lower educational level compared to those who had sought help (Bunting & Boivin, 2007).

We also aimed to investigate the effect of SES on treatment seeking behaviour and pathways of care. In the UK, the cost of infertility treatment could affect use of care by couples from more financially disadvantaged backgrounds, and as such we expected the differences between SES groups would have an effect on progression through the fertility treatment 'system'. Indeed, lack of personal or NHS funding was cited by 23% and 36% of couples, respectively, as a reason for discontinuing IVF treatment in a survey carried out in Scotland (Rajkhowa et al., 2006). Our results did not, however, reveal clear trends in the use of health services for infertility problems according to educational level or SES. However, we did note a

consistent pattern in the data that those women with no qualifications were less likely than those with a degree to consult a doctor, and to have investigations and treatment. Little can be made of this observation because numbers were small in this group and the role of chance cannot be ruled out, but it is worth mentioning as something to consider in future studies. We should also note that our study captured all forms of infertility treatment and not just treatment involving IVF.

Previous studies have reported that middle-class patients are more likely to pursue their goals with the medical profession, spending more time with them and asking more questions (Goddard & Smith, 2001). While this may have an effect, it is also possible that social status is not what affects a couple's use of fertility services, but rather it is their family income, for which SES can be a poor proxy and about which we did not have data in this survey. Our finding that women who had treatment were less likely to conceive a pregnancy if they had no qualifications may be evidence of a persistence in the pursuit of goals for the women with qualifications, but perhaps because they have the income to fund repeated attempts.

Education and social class derived from occupation are the most commonly used indicators of SES. It has been suggested that these two variables measure different phenomena, with one recent study finding only low to moderate correlation between these two indicators (Geyer et al., 2006). It is a strength of our study that we conducted analyses using both education and social class as explanatory factors, particularly given concern that occupation at the time of the last pregnancy may not accurately capture socio-economic position at time of infertility.

There are limitations to this study: it is based on data that may reflect experiences some while ago, however, a more recent study from Scotland has found the prevalence of reported problems conceiving to be similar (Bhattacharya et al., 2009), providing some evidence that our data are still applicable to the current situation in the UK. Although the economic climate and funding provision has changed significantly over that time, it is unlikely that the effect of SES on women's propensity to report difficulties or seek help has.

We also recognise that numbers 'at risk' diminished with progression through the subsets of analysis, commencing with 1486 women who reported ever having fertility problems, and reducing to 1204 who sought medical help, 1019 who had investigations and 615 who had treatment. The statistical power of the study to detect differences in the outcomes analysed across the different social and educational groups (should they truly exist) is reduced accordingly. Nevertheless, we are confident that there was sufficient power (over 80%) to detect a 25% (or greater) decrease in true prevalence of outcome between the highest and lowest levels of education or SES level should it actually exist in the population.

We found that women of higher SES level and with higher levels of education are more likely to report infertility problems. There was no clear evidence that better educated and higher SES women subsequently made more use of fertility services, but, for those who had treatment, the less well-educated women were less likely to achieve a pregnancy. These findings could alert practitioners to the possibility that some of their patients might need more guidance on the recognition of fertility problems to enable prompt access to the help they might need, especially older patients for whom time is imperative.

There is a need for further research in this area which will update estimates and take into account family income in order to explain who uses fertility services to the full, and why. We are currently conducting another cross-sectional survey to collect more recent data on fertility experiences alongside a range of potential confounders. This new survey should provide opportunities to investigate other potential differences such as inequalities in how long women wait before they seek help, as well as looking at the effect of family income.

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Melanie Morris designed this study, cleaned and coded some of the data, analysed and interpreted the data and wrote part of the paper. Laura Oakley cleaned and coded some of the data, analysed and interpreted the data and wrote part of the paper. Noreen Maconochie designed and conducted the original cross-sectional study, cleaned and coded much of the data, interpreted the data and edited drafts of the paper. Pat Doyle designed and conducted the original cross-sectional study, interpreted the data and edited drafts of the paper. The original NWHS was given ethical approval by the Trent Multi-centre Research Ethics Committee and London School of Hygiene & Tropical Medicine Ethics Committee. This study required no additional ethical approval as it was a secondary analysis of the data. This study was completed as part of a PhD funded by LSHTM.

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The epidemiology of infertility: measurement, prevalence and an investigation of early life and reproductive risk factors
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London School of Hygiene and Tropical Medicine
Thesis submitted for Doctor of Philosophy (Nov 2010)

APPENDIX 3
Manuscript on the prevalence of infertility
Oakley 2008
(Paper 1)

Lifetime prevalence c in the UK: results from a population-based survey of reproduction

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BACKGROUND: The aim of this study was to investigate the prevalence of infertility and the use of infertility treatment among women aged 40–55 years. METHODS: Population-based postal questionnaire survey of UK women. Over 60 000 women randomly sampled from the 2001 electoral roll were sent a questionnaire, and those aged 55 years and under who had ever been pregnant or tried to achieve a pregnancy (n = 6584) were asked to provide a reproductive history. RESULTS: Overall, 2.4% of women aged 40–55 years had unresolved infertility with no pregnancies, and a further 1.9% had been pregnant but not achieved a live birth. The prevalence of unresolved fertility did not differ among birth cohorts. Sixteen percent of women reported ever consulting a doctor because of infertility and 8% reported receiving treatment to conceive. Across the whole sample, 4.2% of women reported that they had achieved at least one pregnancy as a result of treatment. Compared with earlier birth cohorts, women born later were more likely to report consultations (18% versus 13%) and treatment (9% versus 6%) for infertility, and pregnancies as a result of infertility treatment (6.7% versus 2.7%). Among those who reported medical consultations, women born more recently first consulted at a later age compared with those born earlier. CONCLUSIONS: Although both the number of women seeking medical care for infertility and the proportion reporting pregnancies as a result of infertility treatment has increased, there is no evidence to support an overall increase in unresolved infertility over the past 15 years. The vast majority of women aged 40–55 who reported difficulties conceiving did have a child, or children, at some point in their lives.

Keywords: infertility; unresolved infertility; infertility treatment; pregnancy; IVF

Introduction

Despite estimates that infertility affects 10–15% of couples in the UK (Evers, 2002), there is a noticeable lack of reliable data on the current lifetime prevalence of infertility and use of infertility treatment in the UK. Previous research has tended to focus on limited samples of those already known to have fertility problems and the few relevant population-based studies that have been carried out in the UK have used small samples or were conducted at least a decade ago (Hull *et al.*, 1985; Templeton *et al.*, 1990; Gunnell and Ewings, 1994). Current information on treatment at a population level is limited to Human Fertilization and Embryo Authority data on the number of cycles of IVF and ICSI performed in the UK (Nyboe Andersen *et al.*, 2007). The proportion of women in the general UK population who have experienced IVF or ICSI, or indeed any type of infertility treatment, is currently unknown.

We report data collected from The National Women's Health Study, a large retrospective population-based study of the reproductive histories of UK women (Maconochie *et al.*, 2004). In this paper, we focus on: (i) the prevalence of unresolved infertility, (ii) the prevalence of reported consultations and treatment for infertility and (iii) the proportion of women who have conceived at least one pregnancy as a result of infertility treatment.

Materials and Methods

Survey

Full details of the study design are reported elsewhere (Maconochie *et al.*, 2004). In brief, this was a population-based postal survey of reproductive histories, designed to enable the construction of a retrospective cohort of reproductive outcome in adult women living in the UK. A random sample of 60 814 women estimated to be under 55 years old at the time of the survey was selected from electronic electoral registers for England, Wales, Scotland and Northern Ireland.

The postal survey had two stages. Stage one consisted of a single-page 'screening' questionnaire which asked for details of all pregnancies experienced by study participants, as well as periods of infertility

and infertility treatment. This form was sent to the whole sample in 2001. The response rate (adjusted for undelivered mail) was 46%, a total of 26 050 questionnaires being returned. Comparison of key reproductive indicators (stillbirth and multiple birth rates and maternal age at first birth) with UK population statistics showed that the data were similar to the general population, and thus that this was a representative population-based sample (Maconochie *et al.*, 2004). The data presented in this paper are from Stage one of the survey only.

Statistical methods

We excluded women who had never been pregnant and had never tried to have a child. For the investigation of infertility in women, we restricted the sample to those women aged 40–55 at the time of the first survey. This is because women at this age are at the end (or nearing the end) of their reproductive years and it enabled us to examine complete, rather than partial, reproductive experience.

Data manipulation and analysis was performed using Stata 9 statistical software (Stata Corporation 2005: college Station, TX, USA). Confidence intervals (CIs) for prevalence estimates were calculated using the binomial distribution, and trends in prevalence by Chi-squared tests for linear trend. *P*-values quoted are two-sided and values <0.05 were taken to indicate statistical significance.

Ethical approval

The study received approval from the Trent Multi-Centre Research Ethics Committee and the Ethics Committee of the London School of Hygiene and Tropical Medicine.

Results

Prevalence of unresolved infertility, or childlessness

A total of 6584 women were aged 40–55 at the time of the survey and stated that they had either been pregnant or had tried to get pregnant. Of these, 159 (2.4%, 95% CI 2.0–2.8) had failed to achieve any pregnancy, despite trying. A further 120 women had only ever had pregnancies which ended in miscarriage or other adverse outcome. Thus, a total of 279 (4.2%, 95% CI 3.8–4.8) women failed to achieve a live birth despite trying. There was no evidence for a birth cohort effect in the prevalence of unresolved infertility where no pregnancy was achieved (primary unresolved infertility) (Table I, *P*-value for trend = 0.94) or in the prevalence of unresolved infertility where pregnancies had occurred but no live birth resulted (Table I, *P*-value for trend = 0.35).

Ever consulting a doctor for problems conceiving and ever having infertility treatment

About 16% ($n = 1045$) of women aged 40–55 reported that at some point in their life they had consulted a doctor about problems conceiving, and 8% ($n = 531$) had received fertility treatment (Fig. 1). There was a strong birth cohort effect in both measures: of women born 1945–1949, 13% had consulted a doctor and 6% had received fertility treatment, whereas 18% of women born 1960–1962 had consulted a doctor and 9% had received fertility treatment at some point in their lives (*P*-values for trend = 0.0005 and 0.0002, respectively).

The mean age at first consultation for all women consulting was 29.7 years, and for those who went on to receive treatment it was 29.8 years (Table II). There was a trend with birth cohort, with women born later consulting at older ages. For women born 1945–1949, the mean age at consultation was 28.4 years for all those who had consulted a doctor, and 29.1 years for those who had received treatment. This compared with 30.8 and 30.5 years, respectively, for women born 1960–1962.

Ever conceiving a pregnancy as a result of fertility treatment

Overall, 4.2% of women reported conceiving at least one pregnancy as a result of fertility treatment (Table III). There was

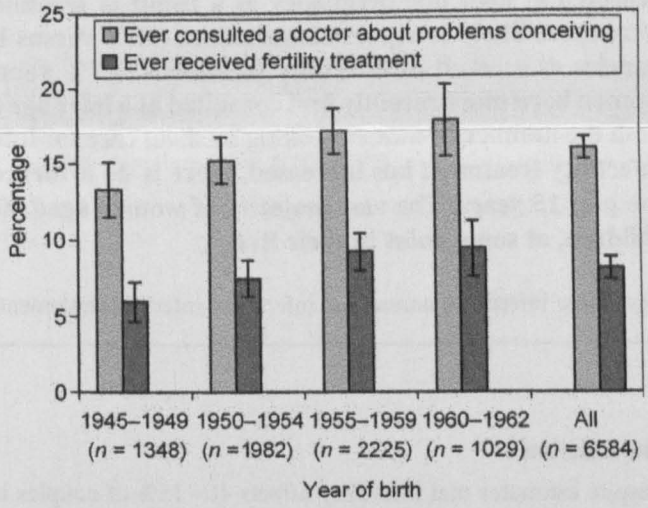

Figure 1: Proportion of women aged 40–55 years at survey who reported ever consulting a doctor about problems conceiving, and who reported ever receiving fertility treatment to help achieve a pregnancy, by year of birth

Table I. Prevalence of involuntary childlessness in women aged 40–55 years by birth cohort.

	Total	Never pregnant		Total	Never live birth	
	N	*n*	Prevalence % (95% CI)	*N*	*n*	Prevalence % (95% CI)
Year of birth						
1945–1949	1348	36	2.7 (1.8–3.5)	1328	55	4.1 (3.1–5.2)
1950–1954	1982	40	2.0 (1.4–2.6)	1952	72	3.7 (2.8–4.5)
1955–1959	2225	60	2.7 (2.0–3.4)	2203	110	4.6 (4.1–5.9)
1960–1962	1029	23	2.2 (1.3–3.1)	1006	42	4.2 (2.9–5.4)
All women	6584	159	2.4 (2.0–2.8)	6489[a,b]	279	4.3 (3.8–4.8)

[a]Excluding 38 women who said they had been pregnant but left outcome blank, and 1 women currently pregnant with her first child.
[b]Excluding 56 women who had only ever had terminations for non-medical reasons and never consulted a doctor about fertility problems.

strong evidence of a trend with birth cohort (*P*-value for test for trend $P < 0.001$), with the proportion of women reporting at least one pregnancy resulting from fertility treatment rising from 2.7% of women born 1945–1949 to 6.0% of women born 1960–1962.

Discussion

In this study of 6584 UK women aged ≤55 years who had ever tried to become pregnant, we found that 4 in 100 women reported that they were involuntarily childless at the end of their reproductive life. Approximately half of these women had been pregnant, but these pregnancies had not resulted in live births. Therefore, 2.4% of the overall sample experienced primary unresolved infertility. Our data provided no evidence for an increasing proportion of reported unresolved infertility with birth cohort. A study in Somerset conducted in the early 1990s reported 2.2% primary unresolved infertility (no pregnancies conceived) and 3.0% unresolved infertility with pregnancies but no live births (Gunnell and Ewings, 1994). Around the same time, 3.5% of a sample in Aberdeen aged over 45 years reported primary unresolved infertility (Templeton *et al.*, 1991). A small study in Shropshire conducted later in the mid 1990s reported 2.4% for primary unresolved infertility and 2.8% for unresolved infertility with pregnancies but no live births (Buckett and Bentick, 1997). Similar prevalences have been found in other Western European countries. Unresolved infertility with no births was reported by 2.6% of Norwegian women aged 40–42 in the early 1990s (Sundby and Schei, 1996), and 4% of Danish women aged 40–45 in an earlier study carried out in 1979 (Rachootin and Olsen, 1982). Overall, available data provide little or no support for the hypothesis of an increasing trend in unresolved infertility over time.

Around 1 in 6 of our sample of women reported difficulties conceiving, and 1 in 12 had consulted a doctor for this reason, at some time in their lives. Our data support previous reports of a birth cohort effect in medical consultations for problems conceiving, with women in the later cohorts (i.e. the younger women in the study) being more likely to seek advice and treatment than those born earlier (Templeton *et al.*, 1990). This is likely to be associated with greater acceptability of infertility and infertility treatment. Women born in the later cohorts consulted on average at a slightly later age, consistent with demographic patterns of later childbearing. A similar trend was observed in the proportion of women reporting that they had experienced at least one pregnancy as a result of infertility treatment. More than twice as many women born 1960–1962 compared with 1945–1949 reported at least one pregnancy conceived as a result of treatment. Whether these women would have contributed to a rise in prevalence of unresolved infertility if they had not had treatment to aid conception is a

Table II. Age at first consultation for women aged 40–55 years who had ever consulted a doctor about problems conceiving and those that had received treatment to help them conceive, by year of birth.

	Year of birth									
	1945–1949		1950–1954		1955–1959		1960–1962		All women[a]	
	All consulted *n* (%)	Received treatment *n* (%)	All consulted *n* (%)	Received treatment *n* (%)	All consulted *n* (%)	Received treatment *n* (%)	All consulted *n* (%)	Received treatment *n* (%)	All consulted *n* (%)	Received treatment *n* (%)
Total no. of women	140 (100)	76 (100)	223 (100)	140 (100)	290 (100)	187 (100)	137 (100)	83 (100)	790 (100)	486 (100)
Age (years)										
<30	96 (68.6)	50 (65.8)	139 (62.3)	85 (60.7)	157 (54.1)	104 (55.6)	67 (48.9)	43 (51.8)	459 (58.1)	282 (58.0)
30–34	24 (17.1)	12 (15.8)	45 (20.2)	27 (19.3)	67 (23.1)	39 (20.9)	34 (24.8)	18 (21.7)	170 (21.5)	96 (19.8)
35–39	14 (10.0)	9 (11.8)	27 (12.1)	22 (15.7)	48 (16.6)	34 (18.2)	29 (21.2)	21 (25.3)	118 (14.9)	86 (17.7)
≥40	6 (4.3)	5 (6.6)	12 (5.4)	6 (4.3)	18 (6.2)	10 (5.3)	7 (5.1)	1 (1.2)	43 (5.4)	22 (4.5)
Mean (SD)	28.4 (5.46)	29.1 (5.83)	29.1 (5.64)	29.3 (5.61)	30.1 (5.95)	30.1 (5.86)	30.8 (5.36)	30.5 (5.23)	29.7 (5.73)	29.8 (5.69)

[a]Two hundred and fifty-five women had missing age at consultation: 39 (22%), 79 (26%), 91 (23%) and 46 (25%) of those born in <1950, 1950–1954, 1955–1959 and 1960–1962, respectively.

Table III. Proportion of women aged 40–55 years reporting at least one pregnancy conceived as a result of infertility treatment, by year of birth.

	Total	Ever conceived a pregnancy as a result of fertility treatment		
	N	*n*	Prevalence %	(95% CI)
Year of birth				
1945–1949	1312	35	2.7	(1.8–3.5)
1950–1954	1941	75	3.9	(3.0–4.7)
1955–1959	2164	103	4.8	(3.9–5.6)
1960–1962	1006	60	6.0	(4.5–7.4)
All women[a,b]	6423	273	4.2	(3.7–4.7)

[a]All women aged 40–55 who reported at least one pregnancy.
[b]Two women (one born 1950–1954 and one born 1955–1959) did not provide information on whether reported pregnancies resulted from fertility treatment.

pertinent, but complex, question. The possible decline of human fecundity is a topical issue, and there has been an interesting recent debate in the literature concerning evidence, or the lack of it, from time-to-conception studies (Sallmen *et al.*, 2005). It is plausible that factors such as exposure to environmental chemicals or simply delayed childbearing are contributing to a decline in fecundity, with the increased accessibility and success of infertility treatment masking this trend and leading to a stabilization in the proportion of women with unresolved infertility. The alternative explanation is that a growing proportion of women seeking infertility treatment would otherwise conceive spontaneously without the aid of treatment. The authors are currently investigating the impact of treatment on the prevalence of unresolved infertility using modelling techniques and will be reporting on this in due course.

Conclusions

The results of this study confirm that a significant proportion of women aged 40–55 have experienced problems conceiving at some point and have sought advice and treatment as a result. Our figures suggest that women from more recent birth cohorts are more likely to seek both advice and treatment for infertility compared with those from earlier birth cohorts, with this trend being accompanied by an increase in mean age at first consultation among more recent birth cohorts. Despite the apparent increase in treatment-seeking behaviour, there is no evidence for an increase in the proportion of women experiencing unresolved infertility with successive birth cohorts. These trends may result from declining fecundity alongside increased acceptability and success of treatment, or they may be explained by a growing proportion of women seeking treatment unnecessarily.

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